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

Peter H Groves, Neil P Lewis, Shahid Ikram, René Maire, Roger J C Hall

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—Mitrail 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) cm) and the incidence of paradoxical septal motion (9/9 v 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) v 12·7 (7·2–16·0) min, p < 0·01), maximum oxygen consumption (11·2 (7·3–17·8) v 17·7 (11·8–21·4) ml min⁻¹ kg⁻¹, p < 0·01), and anaerobic threshold (8·3 (4·6–11·4) v 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 (29·9–59·5) v 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 function, 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 influenced 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 examined 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:

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

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 semi-quantitative 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,9 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 mass spec-
trometry (AirSpec 2000, Biggin Hill, UK) by
means of the argon dilution technique.10 Min-
ute oxygen consumption (VO₂, ml min⁻¹ kg⁻¹),
minute carbon dioxide production (VO₂, ml
min⁻¹ kg⁻¹), and minute ventilation (Ve,
l/min) were measured every 15 seconds. Exer-
cise duration and maximal oxygen consump-
tion (defined as the mean oxygen consumption
during the final 30 seconds of exercise) were
recorded. The anaerobic threshold was deter-
ned by computerised analysis of a curve
fitting model of the relation between oxygen
consumption and carbon dioxide production.12
The ventilatory response to exercise was deter-
mined from linear regression analysis of the
relation between minute ventilation and carbon
dioxide production.13 14

ANALYSIS OF RESULTS
All data are reported as medians and ranges.
Results obtained for the two groups were
compared by a Mann-Whitney test for contin-
uous variables and a Fisher exact probability
test for non-continuous variables. A p value of
<0.05 was regarded as statistically significant.

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 fibrilla-
tion 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 signif-
ificant tricuspid regurgitation had an abnor-
mal 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 thick-
ened in six patients with clinically significant
tricuspid regurgitation and in eight patients in
the control group. Tricuspid valve motion,
hower, 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 1 Clinical, preoperative cardiac catheterisation, and surgical details of the two patient groups (median
(range))

<table>
<thead>
<tr>
<th></th>
<th>TR (n = 9)</th>
<th>Control (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>60.0 (53.5-67.7)</td>
<td>62.0 (56.2-67.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/1</td>
<td>8/1</td>
<td></td>
</tr>
<tr>
<td>Symptom duration preoperatively (yr)</td>
<td>2 (1-11)</td>
<td>2 (2-4.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Time after operation (yr)</td>
<td>10.2 (2.8-17.8)</td>
<td>6.3 (3.5-11.8)</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class III + IV preoperatively</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>NYHA class III + IV currently</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dominant mitral valve lesion:</td>
<td></td>
<td></td>
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<tr>
<td>Stenosis</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Regurgitation</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (mm Hg)</td>
<td>35 (25-90)</td>
<td>35 (16-105)</td>
<td>NS</td>
</tr>
<tr>
<td>Good left ventricular contraction</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Organic tricuspid valve disease</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Prosthesis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disc</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Ball and cage</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tissue</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Prosthetic size (mm)</td>
<td>27 (25-31)</td>
<td>29 (25-31)</td>
<td>NS</td>
</tr>
</tbody>
</table>

TR, tricuspid regurgitation.
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 (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 (2.6-4.5)</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>9.0</td>
<td>3.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (mm Hg)</td>
<td>33 (31-53)</td>
<td>27 (26-67)</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 oxygen consumption</td>
<td>41.0 (29.9-59.5)</td>
<td>33.8 (26.8-59.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maximum increase in SBP (mm Hg)</td>
<td>3.0 (-18-30)</td>
<td>22.0 (2.5-50)</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 (7.7-17.8)</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 (7.3-15.3)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

HR, heart rate; RER, respiratory exchange ratio (CO₂ produced: O₂ consumed); SBP, systolic blood pressure; V̇E/V̇CO₂ slope is derived by linear regression and expresses the relation between ventilation (V̇E) and carbon dioxide production (V̇CO₂) 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 hyperpnoea 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 hyperpnoea response to exercise¹⁹ and
Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease

Reduced capacity with presumably the mechanism reductions is, failing right large tricuspid regurgitation is, corroborate evidence developed showed cusp abnormal control group valve tricuspid ous. Neither echocardiography right ventricular valve disease, therefore, valve tricuspid disease.22 develops either patients develop dilatation may abnormality, while it may be of ventricular right if annular detrimental results of replacement.23 evidence of function or in these patients underwent tricuspid four cardiac output early of threshold20 is the heart maxima- thalesh-eshold20 of arterial valve. This conclusion 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.24 25 Traditional methods of assessment both preoperatively and at the time of surgery are imprecise.26 Haemodynamic measurements are of limited value in assessing the severity of tricuspid regurgitation27 26.2 and digital examination of the amount of tricuspid regurgitation present at operation is influenced by many variables which make it unreliable.28 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.26 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 also 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 non-organic tricuspid regurgitation would regress after adequate correction of left sided lesions,29 but it is now recognised that this is often not the case.30 31 Failure to correct significant tricus-
important tricuspid right about the best annuloplasty or that in this.

failure a described tricuspid leaflet, producing anterior eliminating tion."

aroundcular of a described tricuspid ring, that leads to high and unpredictable failure rates.36,37 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 carpentier 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.38 The Carpentier ring procedure produced a better anatomical repair39 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.40 Whichever approach is adopted it seems that the long term prognosis is often poor.41,42 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.39 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 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 ippecacuanha 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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