NATIVE VALVE INFECTIVE ENDOCARDITIS

A TWENTY TWO MONTH PROSPECTIVE STUDY AT GROOTE SCHUUR HOSPITAL WITH SPECIAL REFERENCE TO THE DIAGNOSTIC AND PROGNOSTIC IMPLICATIONS OF DETECTION OF VEGETATIONS BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY

A N MURRAY MBChB, FCP(SA)

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MODERATOR
PROFESSOR P J COMMERFORD

Cardiac Clinic, Department of Medicine,
Groote Schuur Hospital and the
University of Cape Town.

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Were it not for my family - Ann, Simon and Stuart - there would have been no incentive to have undertaken this dissertation.

CONTENTS

SUMMARY

During the 22-month period from January 1987 to October 1988, 275 patients with the diagnosis of suspected native valve infective endocarditis, referred for echocardiographic evaluation of their valves, were identified and prospectively followed up. Echocardiographically detected vegetations were present in 57, and of these 48 had or were subsequently shown to have infective endocarditis. Of the 218 patients without echocardiographically detected vegetations, 15 were subsequently shown to have infective endocarditis.

Of the 63 patients with endocarditis, blood cultures were positive in 25, and negative in 46 (2 not cultured). Cultures were positive in 14 of 46 patients with vegetations, and positive in 11 of 15 patients without demonstrable vegetations.

In patients with vegetations, neurological complications were present in 8 (17%), renal impairment in 12 (25%), and other embolic complications in 8 (12%). The respective figures for patients without detectable vegetations were neurological 4 (27%), renal 3 (20%), and embolic 4 (27%).

The clinical course of patients with and without detectable vegetations did not differ significantly. In patients with vegetations 8 (17%) died, 31 (65%) required surgery, 2 (4%)

died post-operatively, and 7 (14%) remained stable after appropriate antibiotic therapy. In patients without vegetations detected 4 (27%) died, 6 (40%) required surgery, 1 (6%) died post-operatively, and 4 (27%) remained stable after medical therapy ($p>0.05$ in all events).

At surgery and/or post-mortem examination, nearly all patients were found to have macroscopic vegetations even when these were not detected echocardiographically. Only 3 of 43 patients thus examined did not have macroscopic vegetations - in these cases the diagnosis was established histologically.

Echocardiography consistently underestimated the extent of involvement of vegetations found at surgery and post-mortem. Root abscesses were not detected in 6 cases by echocardiography.

Thus in our hands at Groote Schuur Hospital, in the setting of infective endocarditis echocardiography has a sensitivity of 76%, specificity of 95%. The presence of echocardiographically detected vegetations does not influence the clinical course as regards complications (renal, neurological or embolic); nor as regards outcome (mortality and surgery). Most cases of infective endocarditis have macroscopic vegetations at surgery or post-mortem, despite not being detected

echocardiographically.

INTRODUCTION

The clinical diagnosis of infective endocarditis is notoriously difficult. In this evaluation of the usefulness of echocardiography I chose to apply rigid criteria for the diagnosis. The criteria applied require confirmation histologically at post mortem or surgery and are considered to be important in evaluating the true usefulness of the contribution of echocardiography to ht e management of patients considered to have infective endocarditis.

Since the initial report in 1973 by Dillon et al demonstrating vegetations on M-mode echocardiography in patients with infective endocarditis[1], echocardiography has been shown to be a valuable diagnostic aid in patients with suspected infective endocarditis. This has been futher refined with the advent of 2-dimensional echocardiography[2-4]. However there are still conflicting reports as to the sensitivity, diagnostic accuracy, and prognostic implications of detecting vegetations in patients with infective endocarditis.

The sensitivity of detecting vegetations in patients with infective endocarditis varies from 40% to 80% in reported

series[3,5-10]. Many studies have indicated that the patients with infective endocarditis who have the echocardiographic appearance of vegetations on their valves have a higher incidence of embolic complications and a more aggressive clinical course than those without detectable vegetations[5,6,8,10-12]. This seems to be especially true in the case of larger vegetations[6]. Not all studies concur, and a few studies indicate that the echocardiographic detection of a vegetation is not indicative of a worse prognosis[3,9].

The correlation between echocardiographic and surgical or post mortem findings has been reported in only a small number of patients[5,14]. The echocardiographic findings generally correlate well with surgical findings[5]. Inevitably there will be false negative and even false positive echocardiographically detected vegetations, and the reasons for the latter findings remain obscure.

A distinction should be made between the echocardiographic absence of a vegetation and the macroscopic absence of a vegetation as shown at surgery or post-mortem. Strictly speaking, "vegetation negative" endocarditis refers to patients who do not have vegetations on their valves as shown at surgery or post mortem. Echocardiographic vegetation negative infective endocarditis refers to the absence of echocardiographically detectable vegetations. The vegetations may not be present macroscopically (true

negative) or there may well be vegetations present but the echocardiographic examination fails to detect them. In this study analysis is also made of the patients who at surgery or post mortem did not have macroscopic vegetations demonstrable. Echocardiography may not detect vegetations which are in fact present. Explanations for this include an inadequate study, or vegetations which are conceivably isodense to blood, or vegetations less than 2mm in size[1].

Most studies of echocardiographic findings in infective endocarditis have been retrospective. The number of patients included in these studies has generally been small. Infective endocarditis is a relatively common disease in the community served by Groote Schuur Hospital. It was decided to undertake a prospective study of all aspects of echocardiographic findings in patients with proven and suspected infective endocarditis, to attempt to determine the diagnostic and prognostic implications of the echocardiographic detection of vegetations in patients in whom the diagnosis of infective endocarditis was considered.

AIM

The present study was designed to prospectively study patients with the clinical diagnosis of suspected infective endocarditis, referred for echocardiography of native heart valves. Patients with prosthetic heart valves were excluded from study because of the inherent difficulties of detecting vegetations in this group of patients - most prosthetic valves cause multiple echo-reflections which make accurate identification of vegetations almost impossible. The primary aims of this study were :-

1) To assess the diagnostic implications of detecting a vegetation by echocardiography in patients with suspected infective endocarditis; specifically the sensitivity, and specificity of the investigation were determined. The records of patients with either false positive or false negative results were examined in detail to determine why the investigation had failed.

2) The evaluation of the prognostic implications of the presence and absence of a vegetation in those patients who were subsequently shown to have infective endocarditis. In particular the clinical outcome in terms of death, the need for surgery, or successful medical therapy with antibiotics.

3) To determine whether the presence of a vegetation in any way influenced the frequency of clinical complications, in particular

i) renal impairment

ii) neurological complications

iii) arterial embolic complications other than (i) and (ii).

The observational design of the study made it possible to study not only the general features of patients with infective endocarditis, including the mortality of the disease, offending organisms and positive blood culture rate, but also a variety of other aspects relating to the presence of a vegetation in endocarditis, including :-

1) Serial follow up studies of vegetations in patients after successful therapy to establish the time period to disappearance of vegetations after therapy.

2) Comparative study of blood cultures and echocardiographically detected vegetations to assess the relative diagnostic accuracy of these two investigations.

3) Correlation of echocardiographic and surgical (or autopsy) findings.

4) Assessment of the role of surgery in the acute phase of endocarditis.

METHODS

Patient population.

From January 1987 till October 1988 all patients referred to the echocardiography laboratory with a clinical diagnosis of suspected infective endocarditis were identified and prospectively followed. Only patients with native heart valves were included - patients with prosthetic valves were excluded from study because of the inherent difficulties of detecting vegetations on prosthetic valves[10,14]. The echocardiography laboratory provides a service to some 300 medical beds and the outpatient department. All requests from physicians are accepted. During 1987, 1 700 studies were performed.

Echo Study

Standard 2-dimensional echocardiography with an Ultramark 8 scanner, employing a 3,0 MHz transducer, using standard parasternal short and long axis, and apical views were performed on all patients. A vegetation was defined as an echogenic, mobile, discrete mass, present in an abnormal location, mobile, and attached to an underlying intracardiac structure (valve) or chamber wall. Vegetations were described by the echocardiographer as definitely present, probably present, or absent, and unless specifically specified as definitely present or probably present were

considered absent. Reports such as "a vegetation cannot be excluded" were considered as absent vegetations. All studies were reviewed daily by a consultant cardiologist, experienced in echocardiography. His designation was accepted in all cases.

Follow up.

Patients were subsequently followed up until hospital discharge and when necessary beyond their hospital stay. The clinical course of each patient was recorded. Patients diagnosed as having infective endocarditis were subsequently followed up at the Cardiac Clinic, with endpoints being cardiac surgery (valve replacement) or death. Patients who underwent valve replacement were subsequently followed up to assess the recurrence of infection if surgery was performed during active infection before completion of a course of antibiotic therapy.

Patients who responded to antibiotic therapy and did not require surgery, had repeat echocardiographic studies performed at three-monthly intervals to evaluate the natural history of vegetations.

Definitions.

i) Vegetation

A vegetation was defined as an echocardiographically discrete echogenic mass present in an abnormal location,

usually on a heart valve, distinct from the normal cardiac structures. The presence of a vegetation was futher defined as being definite, probable or possible.

ii) Infective Endocarditis.

For a diagnosis of infective endocarditis the criteria of Pelletier and Petersdorf were used[15] (Table 1).

TABLE 1

Criteria for the diagnosis of infective endocarditis (IE).

(1) **Definite** IE: Histologic evidence of infected vegetation(s) from examination of tissue obtained from cardiac surgery, embolectomy, or autopsy.[a]

(2) **Probable** IE: Either uniformly positive blood cultures with known underlying heart disease **and** evidence of emboli to the skin or viscera; or negative blood cultures in individuals with fever (>38'C), new regurgitant valvular heart murmurs, and embolic phenomena.

(3) **Possible** IE: Either uniformly positive blood cultures with known underlying heart disease or embolic phenomena; or negative blood cultures with fever, known underlying heart disease, and embolic episodes.

[a]In the event of histology being obtained which excluded infective endocarditis, the clinical diagnosis of probable or possible endocarditis was ignored in preference to the histological findings.

iii) Histological criteria for the diagnosis of infective endocarditis

A diagnosis of infective endocarditis was considered as

1) Absolute if :-

a) organisms were visualized on gram stain of histological specimens.

b) An acute inflammatory infiltrate was seen in a fibrinous vegetation without the presence of Aschoff bodies.

2) Compatible if:-

a) A chronic inflammatory response was present in the absence of Aschoff bodies, with macroscopic vegetations on the endocardial surface.

iv) Renal impairment

was defined as moderate if the serum creatinine concentration was above 150nmol/l. Severe renal impairment was defined as renal impairment severe enough to require dialysis or if it resulted in the patients death.

v) Embolic event (excluding neurological complications)

was defined as an absent arterial pulse, previously documented as present; or a clinically diagnosed acute arterial occlusion - associated with signs and symptoms of

ischemia; or recurrent pulmonary embolic phenomena in the setting of suspected tricuspid valve endocarditis. Splinter hemorrhages and hematuria were accepted as embolic phenomena for diagnostic purposes, but were not considered as clinically important embolic complications.

DATA COLLECTED

On all patients in whom the clinical diagnosis of infective endocarditis was made, the following information was collected :-

1) general information including age, sex

2) history of present illness:- presenting symptoms, duration, date of diagnosis, precipitating factors, antibiotic therapy prior to presentation.

3) previous cardiac and medical history.

4) clinical examination including fever, peripheral evidence of infective endocarditis, cardiac examination, urine examination, chest X-ray and electrocardiographic findings.

5) laboratory results such as full blood count, erythrocyte sedimentation rate, serum creatinine and urea concentration, blood culture results, Q-fever, chlamydia and brucella serology, VDRL.

6) echocardiographic findings on presentation, follow-up and on discharge at three-monthly intervals until the disappearance of the vegetations.

7) antibiotic therapy

8) clinical course

9) in event of surgery, the date of surgery, indications, findings, histological findings of excised valves, and bacteriological cultures of excised tissue.

10) in event of death, the date, cause, and the autopsy findings if one was performed.

11) post operative complications.

13) post surgical follow-up, and follow-up on all patients till the date of end of the study.

COLLECTION METHODS

Every patient referred to the echocardiography laboratory with the diagnosis of suspected infective endocarditis was prospectively followed up. The patients were seen during the hospital admission at a time by which sufficient data was available to confidently make a clinical diagnosis. When the diagnosis was unclear, the patient was reviewed until the clinical diagnosis became apparent.

Initially as a check to establish whether all cases of infective endocarditis were being referred for echocardiography, all bacteriology blood culture records were reviewed. The names of the patients who had blood cultures sent with a diagnosis of bacterial endocarditis were checked to ensure that they had been referred for echocardiography. After nine months of such review, no

additional cases had been identified and the procedure was discontinued.

The following groups of patients were identified :-

1) patients with infective endocarditis

were subsequently followed up at cardiac clinic, and at the time of the end of this study, the condition of each and every one of these patients was known (100% follow up).

2) patients without infective endocarditis

a) without echocardiographically detected vegetations (true negative). The final diagnoses of all the patients in this group was obtained.

b) with echocardiographically detected vegetations (false positive). Patients in whom vegetations were detected on echocardiography but who did not have enough evidence to diagnose infective endocarditis were also followed up for a prolonged period to establish whether the disease process would still manifest itself or until the cause of the false positive finding became apparent.

3) patients treated by the attending physician for infective endocarditis, without sufficient evidence for such a diagnosis.

STATISTICAL ANALYSIS

Where appropriate, continuous data was analyzed using student's t-test , and Fischer's exact test for discrete data. Data is expressed as mean +-standard deviation.

RESULTS

Total Group

Over the 22 month period, from 1st January 1987 to 31st October 1988, a total of 275 patients with the diagnosis of suspected infective endocarditis were referred to the echocardiography laboratory for assessment of vegetations on their native valves. Of the 275 patients, vegetations were detected echocardiographically in 57 (figure 1). In this group of 57, infective endocarditis was proven to be present in 48. In the 218 patients without echocardiographically detected vegetations, 15 were subsequently shown to have infective endocarditis.

False Positives

In the remaining 9 patients with echocardiographic vegetations but without infective endocarditis, the diagnoses were as follows (figure 2):-

i) rheumatic heart disease - mitral regurgitation with flail leaflets : 4 patients. All 4 underwent valve replacement for severe mitral regurgitation after a period of intravenous antibiotic therapy, for presumed infective endocarditis. Histological examination of excised valve tissue, surgical findings and clinical criteria failed to establish the diagnosis of infective endocarditis.

PRESENCE OF VEGETATIONS

TOTAL PATIENTS

275

57 VEGETATIONS
218 NO VEGETATIONS

FIGURE 1

ii) pneumonia : 2 patients with pneumonia were found to have the echocardiographic appearances of vegetations (one mitral valve, one aortic valve). Both received intravenous antibiotics for the pneumonia. The possibility exists that they may have had infective endocarditis.

iii) large vegetation on the tricuspid valve. Patient was lost to follow up.

iv) lupus endocarditis (Libmann-Sacks) : one patient.

v) ruptured appendix : the presence of the vegetation remained unexplained. This patient received intravenous antibiotics.

True Negative

There were 218 patients who did not have vegetations detected echocardiographically, and 203 were subsequently shown not to have endocarditis. The final diagnoses in this group of patients is shown in figure 3. The most frequent final diagnosis in this group was chronic rheumatic heart disease, (often with an associated upper respiratory tract infection or pneumonia). Acute rheumatic fever also featured prominently - a condition still not infrequently seen in our population group. The remaining more common final diagnoses in this group of patients was sepsis, pneumonia and vasculitis (including systemic lupus erythematosus).

DIAGNOSES IN PATIENTS WITH VEGETATIONS

VEGETATIONS
57 PATIENTS

48 ENDOCARDITIS
4 RHEUMATIC HEART DIS
2 PNEUMONIA
1 TRICUSPID VEGETATION
1 SYSTEMIC LUPUS
1 RUPTURED APPENDIX

FIGURE 2

True Negative - Treated for Infective Endocarditis

In 8 cases, the treating physician felt the patient concerned warranted 6 weeks antibiotic therapy despite insufficient evidence to support for the diagnosis of infective endocarditis according to the criteria described previously.

Three of these eight patients required aortic valve replacement and at surgery had no vegetations or evidence of endocarditis. Two were found to have the appearances of a syphlitic aortitis. In both serology for syphilis was positive, and histological examination of excised aortic valve revealed features compatible with a syphlitic aortitis. The third patient had histological features of acute rheumatic fever.

One patient undergoing mitral valve replacement was found to have an intrapericardial abscess involving the pulmonary conus, but no involvement of either aortic or mitral valve. Blood cultures had grown Klebsiellae, thought to be originating from a pneumonia.

Of the four remaining patients in this group, three had clinical features more supportive of a diagnosis of acute rheumatic fever. Without definite histology or more conclusive laboratory tests in these patients, the differentiation between rheumatic and infective endocarditis

DIAGNOSES IN PATIENTS WITHOUT VEGETATIONS

NO VEGETATIONS
218 PATIENTS

15 ENDOCARDITIS
65 CHRONIC RHD
26 PNEUMONIA
21 VASCULITIS
29 SEPTICEMIA
16 RHEUMATIC FEVER
46 OTHER

FIGURE 3

remains speculative.

The eighth patient in this group died from a fulminant septicemia. Permission for post mortem examination was refused. A definitive final diagnosis is therefore not possible.

PATIENTS WITH INFECTIVE ENDOCARDITIS (63 patients).

GENERAL CHARACTERISTICS

The general characteristics of patients with infective endocarditis are displayed in appendix 1.

1) Age : The mean age of the patients was 37 years with a range from 10 to 75 years (only 3 over 65 years).

2) Sex : There were 39 males, 24 females.

3) Symptom duration : The mean time from onset of symptoms (which is sometimes difficult to establish) to diagnosis was almost 6 weeks. The most common presenting symptom was shortness of breath on exertion (40/63 = 63%). In patients with underlying valve lesions a deterioration in previously impaired effort tolerance was the equivalent symptom. Other presenting symptoms included neurological problems, malaise and fever. One patient was found to have infective

endocarditis during a routine pre-employment medical examination.

4) Underlying lesions : The most common underlying cardiac lesion was rheumatic heart disease 33 (52%). Other lesions included mitral valve prolapse 7 (11%), and congenital heart disease 4 (6%). However, in 18 (29%), no pre-existing underlying heart lesion could be identified.

5) A precipitating factor could only be identified in 6 patients. Only 2 patients had had a recent dental extraction without antibiotic cover. It is difficult to assess the significance of poor oral hygiene as a precipitating factor. Other significant precipitating factors included long term indwelling central lines and chronic sepsis. Two cases followed penetrating cardiac trauma (knife wounds).

6) Referral hospital : As Groote Schuur is a referral centre, many cases of infective endocarditis were referred from other centres. The various sources are shown in table 2. Where appropriate, this confounding factor is taken into account (eg. blood culture positivity rate). The general characteristics of these patients compared to patients presenting directly to Groote Schuur is shown in table 3.

TABLE 2 : Number of patients referred from other centres.

Referring Centre	Number Patients
Frere Hospital	11
Kimberley Hospital	3
Somerset Hospital	2

One patient from each of the following centres :-
Conradie, Livingstone, George, Beaufort West, Mauritius.

The age of the referred patients was slightly younger than the Groote Schuur patients. Underlying valve pathology (rheumatic heart disease etc.) was similar in both groups, with slightly more congenital lesions in the referred group of patients. The blood culture positivity rate was significantly lower in the referred patients, and no cases of Staphyllococcus aureus were found. The presence of vegetations was similar. There were no cases of right-sided endocarditis in the patients referred from other centres, and slightly more cases of aortic valve endocarditis as compared to the Groote Schuur hospital patients.

The complication rate (neurological, renal, embolic) in the two patient groups were almost identical. However as far as the outcome is concerned, most patients had been referred

TABLE 3 : PATIENT CHARACTERISTICS FROM OUTLYING CENTRES

	REFERRED	GROOTE SCHUUR	p-VALUE	TOTAL
Number	23	40		63
Age	31(+-14)	41(+-17)		
Sex (M:F)	1,9:1	1,4:1	NSS	
VALVE: RHD	13 (57%)	20 (50%)	NSS	33(52%)
Normal	4 (17%)	14 (35%)	NSS	18(29%)
Other	6	6	NSS	12
CULTURE (pos)	5 (22%)	20(53%)n=38	<0,0005	25(41%)
Strep	2	11		
Staph aureus	0	5		
Other	3	4		
VEG: Definite	19 (83%)	29 (73%)	NSS	48(76%)
Probable	3 (13%)	4 (10%)		7 (11%)
Absent	1 (4%)	7 (17%)		8 (13%)
VALVE:Mitral	8 (35%)	16 (40%)	NSS	24 (38%)
Aortic	13 (57%)	15 (37,5%)	NSS	28 (44%)
Both	2 (8%)	4 (10%)	NSS	6 (11%)
Right-side	0	5 (12,5%)		5 (8%)
COMPL:Renal imp	5 (22%)	10 (25%)	NSS	15 (24%)
Neuro	4 (17%)	8 (20%)	NSS	12 (19%)
Embolic	4 (17%)	8 (20%)	NSS	12 (19%)
OUTCOME:Medical	2 (9%)	9 (22,5%)	NSS	11 (17%)
Surgical	19 (82%)	18 (45%)	<0,05	37 (59%)
Death	2 (9%)	10 (25%)	<0,05[1]	12 (19%)
Post-op death	0	3 (7,5%)		3 (5%)

[1]Post-op deaths included. NSS:not statistically significant

for surgical evaluation, and thus surgery was performed in the majority (19/23=82%). The mortality rate in the referred group was low (9%).

BLOOD CULTURES

The results of the blood cultures and the specific organisms isolated are shown in table 4. For the purposes of discussion patients with positive serology (Q-fever and Chlamydia) were included with the blood culture positive group (organism identified). The incidence of positive blood cultures in the patients in whom echocardiographic vegetations were present and absent is shown in figure 4a. Figure 4b illustrates the Groote Schuur patients results concerning blood cultures and the presence or absence of vegetations. The positive blood culture rate overall is 41%. However patients referred to Groote Schuur from other centres had a positive culture rate of 22%, whereas patients presenting directly to Groote Schuur had a culture positive rate of 53%.

In the Groote Schuur patients (referred patients excluded) 53% had positive blood cultures. Blood cultures were more frequently positive in patients in whom vegetations were not demonstrated (73%). The figures for the referred patients is even more impressive - 22% and 75% respectively.

TABLE 4

BLOOD CULTURE ISOLATES, PRESENCE OF VEGETATIONS AND OUTCOME OF THE PATIENT

ORGANISM	VEGETATION[1]			OUTCOME[2]			TOTAL
	DEF	PROB	ABS	MED	SURG	DIED	
Streptococcus	9	2	2	3	7	3	13
Staph. aureus	2	1	2	0	2	3	5
epiderm.	1	-	-	1	-	-	1
Hemoph. parainf	1	-	-	1	-	-	1
Neisseria gon.	-	1	-	-	1	-	1
Chlamydia	-	-	1	-	1	-	1
Corynebacterium	-	-	1	-	1	-	1
Candida alb.	-	1	-	1	-	-	1
Q-fever	1	-	-	-	-	1	1
TOTAL	14	5	6	6	12	7	25

[1]DEF:definite; PROB:probable; ABS:absent

[2]MED:medical; SURG:surgical

However it is difficult to draw any conclusions from these figures as there is no data concerning infective endocarditis in patients not referred to Groote Schuur hospital from outlying centres.

The most common organism cultured was the Streptococcus (52% of positive cultures), followed by Staphyllococcus (24%).

PRESENCE OF VEGETATIONS AND BLOOD CULTURES

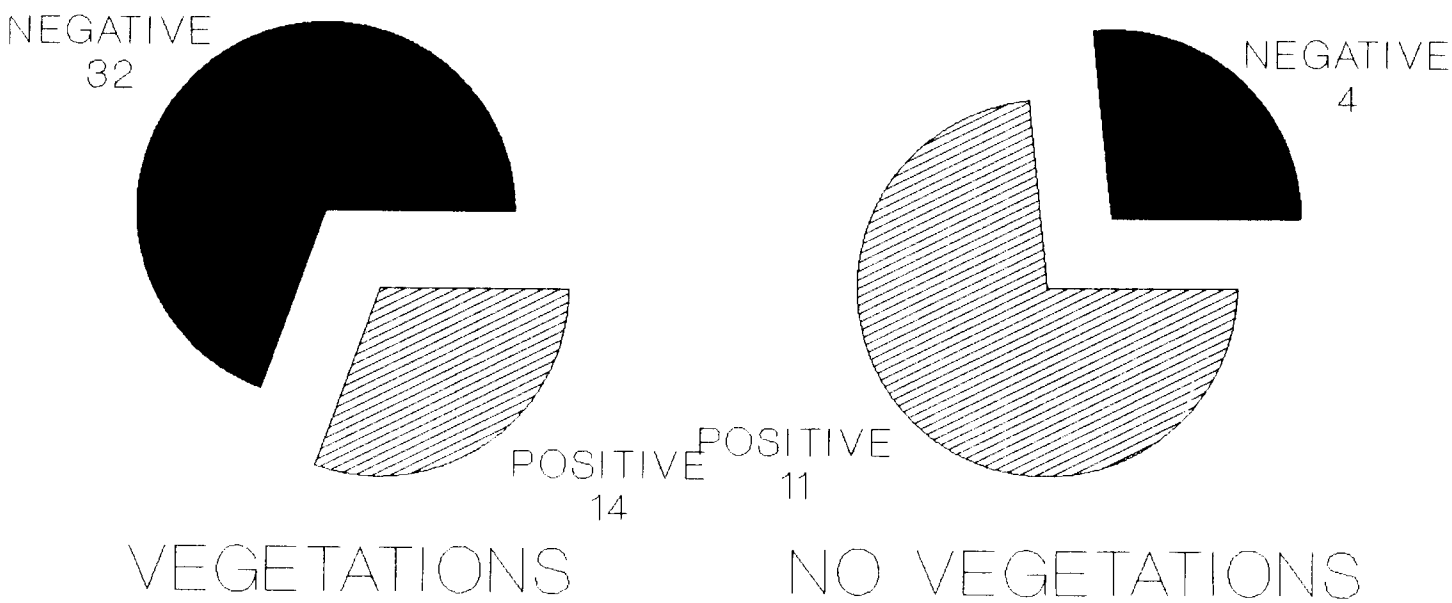


FIGURE 4

VEGETATIONS AND CULTURES IN REFERRED PATIENTS

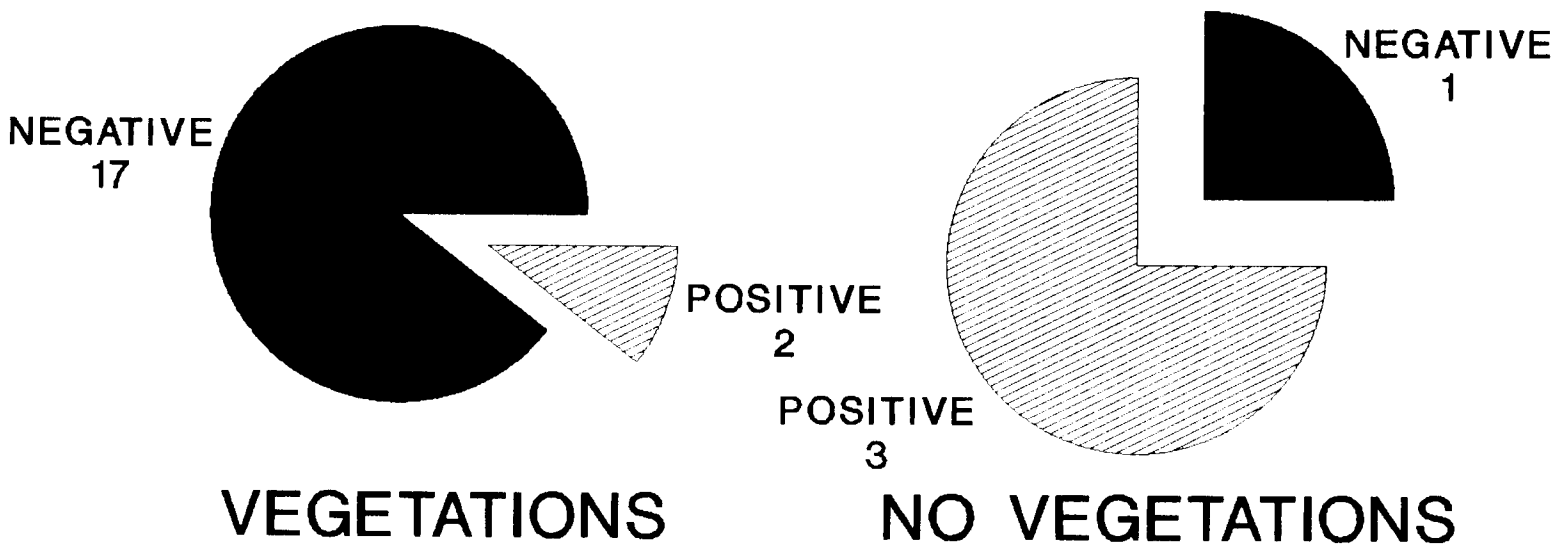


FIGURE 4a

VEGETATIONS AND CULTURES IN GROOTE SCHUUR PATIENTS

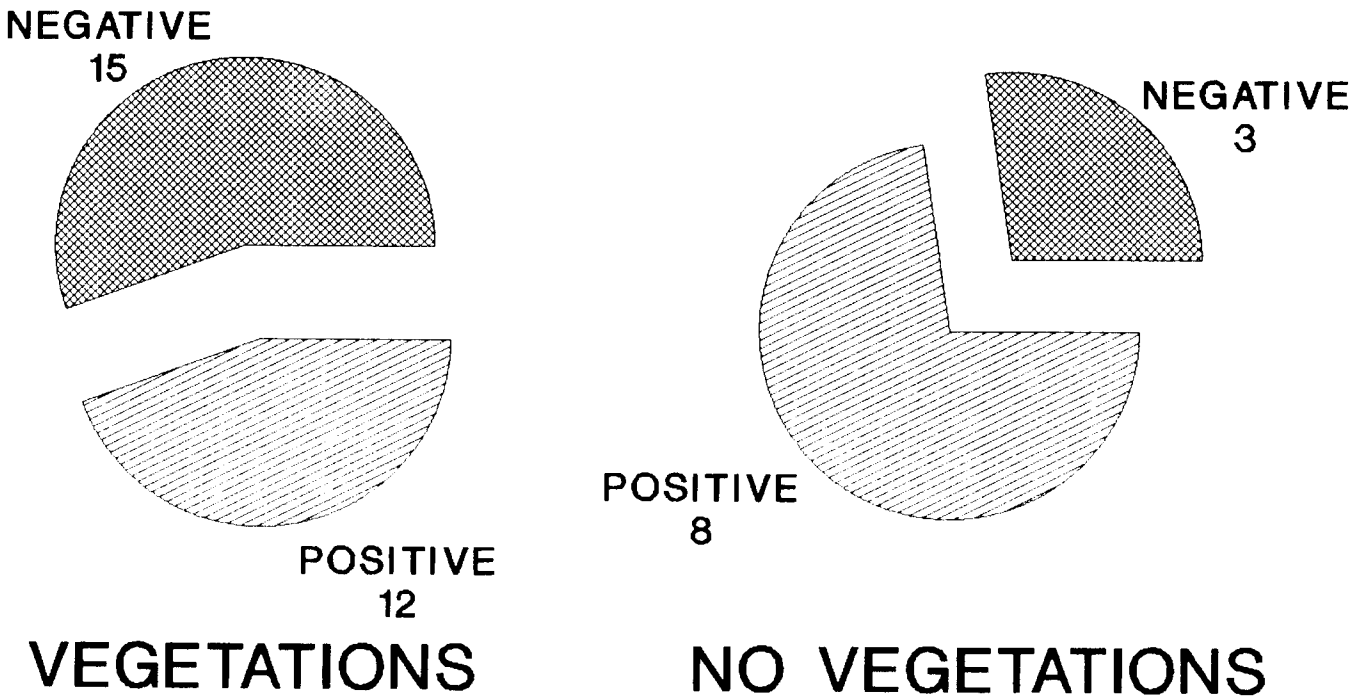


FIGURE 4b

Other single isolates included Neisseria gonorrhea Candida albicans, Hemophillus parainfluenza and Corynebacterium. Of the 12 patients who died, 7 had a positive blood culture, three of them being Staphyllococcus aureus. Two patients with Staphyllococcus aureus cultured, survived - both required valve replacement.

There was one case of Q-Fever endocarditis and one chlamydial endocarditis. In most blood culture negative cases of endocarditis, a screen of chlamydial, Q-Fever and brucella serology was perform[ed]. The patient with chlamydial endocarditis had no echocardiographically detected vegetations, but at surgery had large vegetations on the aortic valve. Immunofluorescent studies were performed on excised valve tissue, as suggested by an earlier report[16], but these studies were negative. However, as this investigation had not previously been performed by our laboratory, the validity of the test is uncertain.

The patient with Q-Fever endocarditis was treated with a protracted course of antibiotics. The follow-up echocardiographic studies revealed that the vegetations diminished in size and after (6) months were not detected. However, three months after the vegetations were undetectable on echocardiography, the patient returned moribund, was found to have large vegetations detected on echocardiography, and died soon after readmission. Post-

mortem confirmed large vegetations on the mitral valve.

VALVE LOCATION

The mitral valve was affected in 25 cases (40%), the aortic valve in 27 (43%), and both aortic and mitral in 6 (9%). There were only 3 cases of tricuspid valve endocarditis, a single case of pulmonary valve endocarditis and one case of combined pulmonary and tricuspid endocarditis. The site of the echocardiographically detected valve involved is depicted in table 5.

VEGETATION	Mitr	Aor	Mi&Ao	Tric	Pulm	Tr&pu	Total
Definite	16	23	5	2	1	1	48
Probable	2	3	1	1	0	0	7
Absent	6	2	0	0	0	0	8
TOTAL	24	28	6	3	1	1	63

TABLE 5

Valve Involved and Presence of Vegetation

TRICUSPID AND PULMONARY VALVE IE

There were three cases of tricuspid valve, one of pulmonary valve, and one case of combined pulmonary and tricuspid valve infective endocarditis. Three of these cases were precipitated by prolonged insertion of central lines (for total parenteral nutrition). One case followed penetrating trauma, and the fifth case was related to a ventricular septal defect. The underlying heart valves in all cases were thus considered to be "normal". Two of the patients improved after removal of the central lines. The two patients with pulmonary valve involvement required pulmonary valve replacement. One patient with tricuspid endocarditis had numerous other medical problems and the endocarditis was secondary to prolonged use of indwelling central lines. This patient eventually died of septicemia. No case of endocarditis secondary to intravenous drug abuse was present in this series.

CLINICAL OUTCOME : COMPARISON BETWEEN PATIENTS WITH AND THOSE WITHOUT VEGETATIONS DETECTED ECHOCARDIOGRAPHICALLY.

The clinical outcome of the two patient groups (those with and without vegetations detected echocardiographically) are depicted in figure 5. Characteristics of the patients are tabulated in table 6.

PATIENTS REQUIRING VALVE REPLACEMENT

In the patients with infective endocarditis, 40 (63%) underwent surgery (valve replacement). In a futher 5 surgery was recommended surgery but refused - three of these patients have died from cardiac failure. The indications fór surgery were cardiac failure in 32 (80%), uncontrolled infection in 6 (15%), and recurrent emboli in 2 (5%). The presence or size of a vegetation per se was NOT an indication for surgery. In 8 (20%) surgery was performed as an emergency - within 14 days of diagnosis, and still in the acute phase in 9 (22,5%) - defined arbitrarily as having had less than 6 weeks antibiotic therapy. In 13 (32,5%) surgery was performed after 6 weeks of intravenous antibiotics. In a futher 8 (20%) surgery was performed after completing medical treatment - ie for subsequent hemodynamic deterioration of the damaged valve.

INFLUENCE OF VEGETATIONS ON CLINICAL OUTCOME

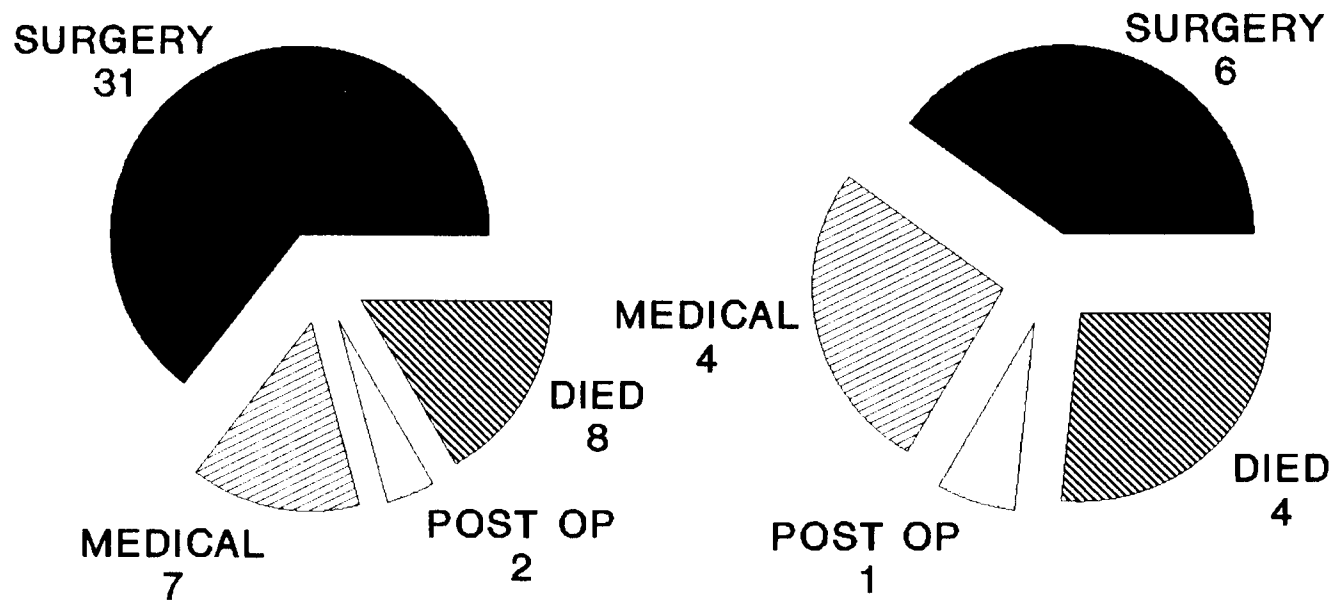


FIGURE 5

OUTCOME IN REFERRED PATIENTS

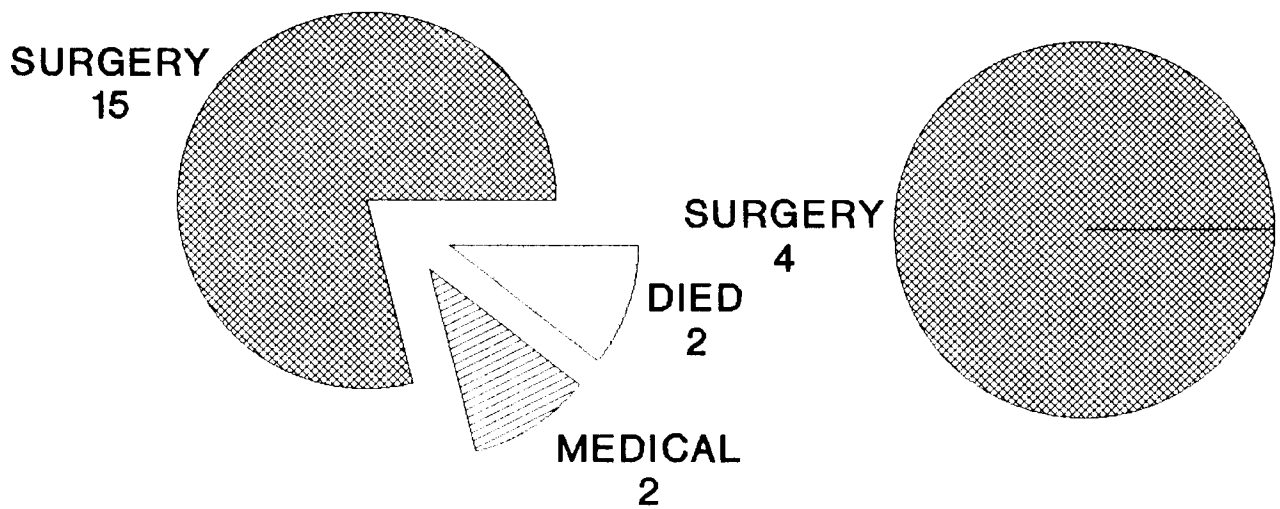


FIGURE 5a

OUTCOME IN PATIENTS FROM GROOTE SCHUUR

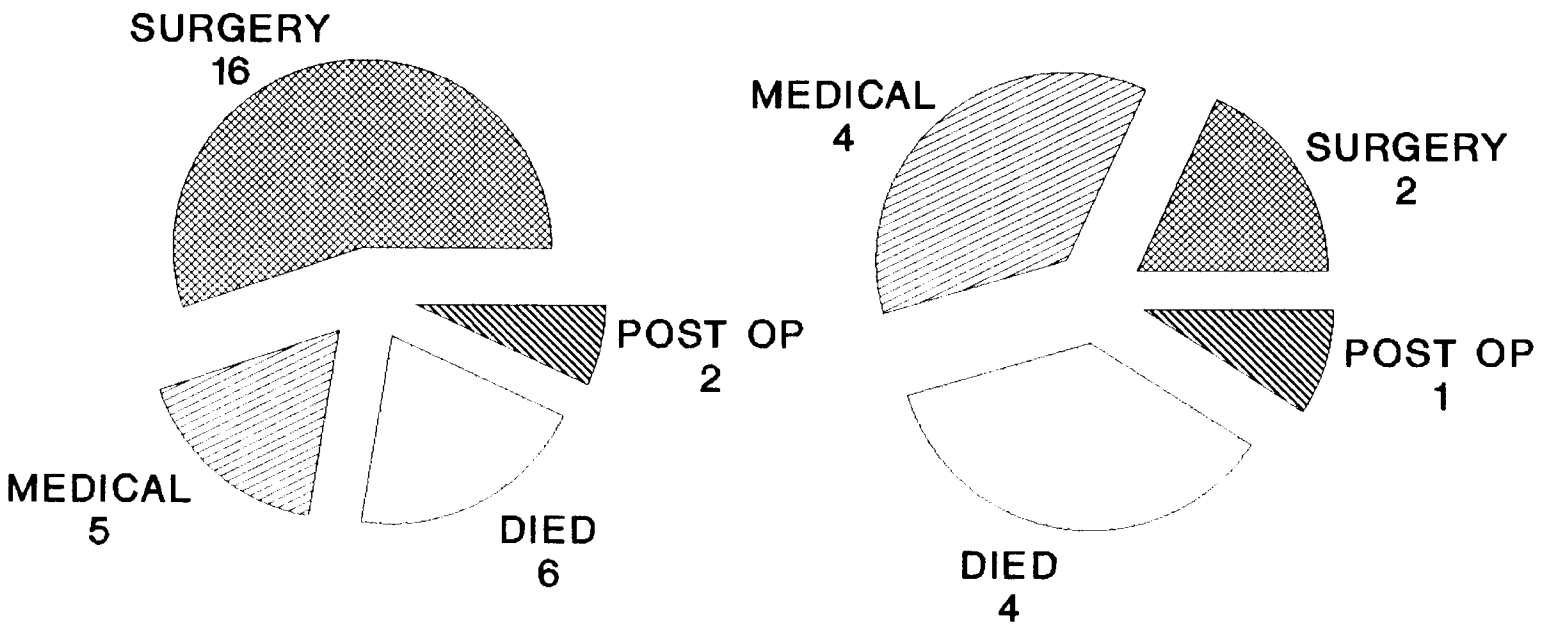


FIGURE 5a

In patients with vegetations (total 48), 33 (69%) underwent surgery, indications being cardiac failure in 28, infection 4, and emboli in one. Emergency surgery was required in 8 and before completion of medical therapy in a futher 4.

In patients without vegetations, surgery was performed in 7 (47%), indications being cardiac failure in 4, infection 2, and emboli in one. One was performed as an emergency, and three before 6 weeks antibiotic therapy.

There was no statistical difference with regard to the need for valve replacement surgery between those with and without vegetations.

DEATHS

Fifteen patients with definite infective endocarditis died (mortality rate 24%). Ten patients with vegetations (21%) and five without vegetations died (33%). While the mortality rate in patients without echocardiographically detected vegetations is slightly higher, the differences are not statistically significant ($p<0,254$).

There were three peri-operative deaths. One patient died on the 5th postoperative day due to rupture of a previously asymptomatic cerebral mycotic aneurysm. A second death

occurred intraoperatively when the patient could not be weaned from cardiopulmonary by-pass. The third patient succumbed to septicemia, which had been the primary indication for the valve replacement.

One non-cardiac death was recorded in a patient who died of disseminated adenocarcinoma several months after valve replacement .

RESULTS OF MEDICAL TREATMENT

Eleven patients have completed 6 weeks of antibiotic therapy and have not yet required valve replacement. Two patients have been advised surgery but declined. Mean follow up for this group is 8 months , with a range of 3 to 18 months. This group consists of 7 patients with definite echocardiographic vegetations (15% of patients with vegetations), and 4 without (27%)($p<0,240$).

It is noteworthy that these patients in whom medical therapy was successful had a shorter duration of symptoms (7 days) prior to diagnosis than those who needed surgery (64 days), or than those who died (21 days).

Also, in this group, the mitral valve was more frequently involved than the aortic (7 vs 1), whereas the tricuspid valve was involved in two cases, and both aortic and mitral

in one.

TABLE 6

CHARACTERISTICS OF PATIENTS WITH AND WITHOUT ECHOCARDIOGRAPHICALLY DETECTED VEGETATIONS

	VEGETATION		p-VALUE	TOTAL
	PRESENT	PROB/ABS		
Number	48	15		63
Age	35(+-15)	46(+-17)		37(17)
Sex (M:F)	2:1	7:8	NSS	
Valve: RHD	28 (58%)	5 (33%)	NSS	33 (52%)
Normal	13 (27%)	5 (33%)	NSS	18 (29%)
Other	7 (15%)	5 (33%)	NSS	12 (19%)
Culture (pos)	14 (30%)	11 (73%)	<0,004	25 (41%)
Strep	9	4		13
Staph au	2	3		5
Other	3	4		7
VALVE: Mitral	16 (33%)	8 (53%)	NSS	24 (38%)
Aortic	23 (48%)	5 (33%)	NSS	28 (44%)
Both	4 (8%)	2 (14%)	NSS	6 (10%)
Right-side	5 (11%)	0		5 (8%)
Complication				
Renal imp	12 (25%)	3 (20%)	NSS	15 (24%)
Neuro	8 (17%)	4 (27%)	NSS	12 (19%)
Embolic	8 (17%)	4 (27%)	NSS	12 (19%)
OUTCOME:Medical	7(14%)	4 (27%)	NSS	11 (17%)
Surgical	31 (65%)	6 (40%)	NSS	37 (59%)
Death	8(17%)	4 (27%)	NSS	12 (19%)

Post-op death	2(4%)	1 (6%)	NSS	3 (5%)

RENAL FUNCTION

Ideally renal function should be assessed by meticulous 24-hour creatinine clearances. This data is not available on all the patients. The method of assessing renal function employed in this study, using the serum creatinine concentration has its limitations, but nonetheless does give some indication as to the incidence of renal impairment in the patients with and without echocardiographically detected vegetations. For purposes of this study, moderate renal impairment was defined as a serum creatinine concentration of above 150nmol/l. Severe renal impairment was indicated by the need for dialysis or renal failure resulting in the death of the patient.

The incidence of renal function impairment in patients with and without echocardiographically detected vegetations is depicted in figure 6, and the characteristics of the individual patients in appendix 2.

One patient had been treated with plasmaphoresis for acute glomerulonephritis prior to the diagnosis of endocarditis. In retrospect this patient probably had infective endocarditis presenting as an acute crescentic glomerulonephritis as shown on biopsy (the only patient of the group to undergo renal biopsy). Interestingly the patient's renal function improved after plasmaphoresis

INFLUENCE OF VEGETATIONS ON RENAL IMPAIRMENT

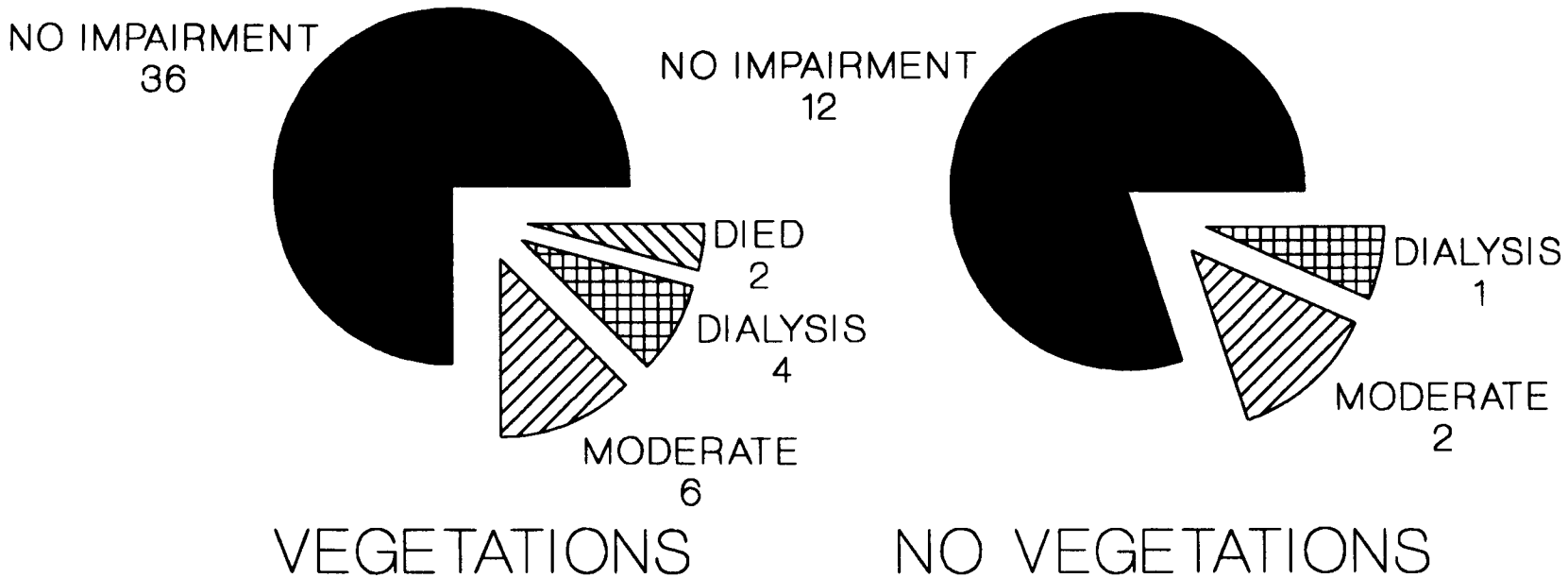


FIGURE 6

despite not having had any therapy for his underlying endocarditis, and it was only later that the patient was found to have significant underlying aortic regurgitation due to endocarditis with vegetations detected echocardiographically and confirmed at surgery.

The specific valve location did not have an influence on the incidence of renal impairment. The mitral valve was involved in 6 patients aortic in 7, and combined in one. Blood cultures were positive in 5 cases (33% of patients with renal impairment).

Of the patients with renal impairment 2 died as a consequence of the renal failure, 4 died from other complications and all the remaining 9 patients required valve replacement.

Vegetations were not detected on echocardiography in 3 patients with renal impairment. One of these required dialysis but died in the post-operative period. In patients with echocardiographically demonstrated vegetations who had renal impairment (12 patients), dialysis was performed in 4, and 2 died from their renal failure. The number of patients with significant renal impairment is too small to detect any statistical significance between the patients with and without echocardiographic vegetations ($p<0,494$).

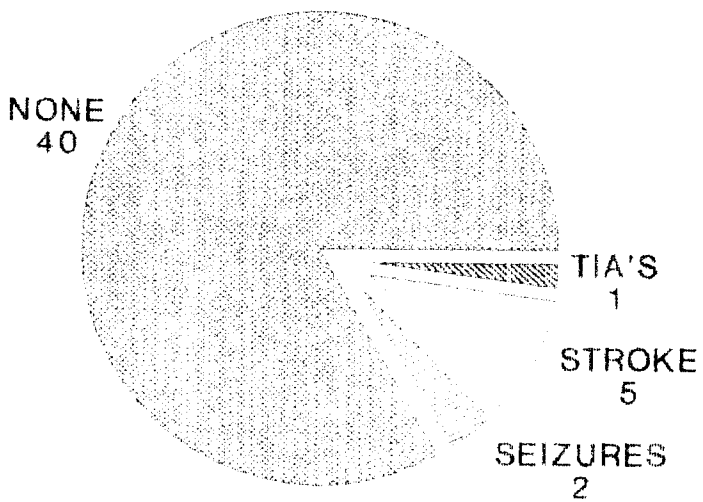
MAJOR NEUROLOGICAL COMPLICATIONS.

The various neurological complications that occurred are shown in table 9. Major neurological complications were defined as permanent neurological deficits resulting as a direct consequence of infective endocarditis, and included embolic stroke, intracerebral hematoma, subarachnoid haemorrhage and seizure activity. Neurological complications were the presenting feature in nine patients. Three patients developed their complications only after the diagnosis of endocarditis had been established and therapy commenced. One of these patients who had been asymptomatic post valve replacement collapsed and died. At post mortem he was shown to have a large subarachnoid hemorrhage.

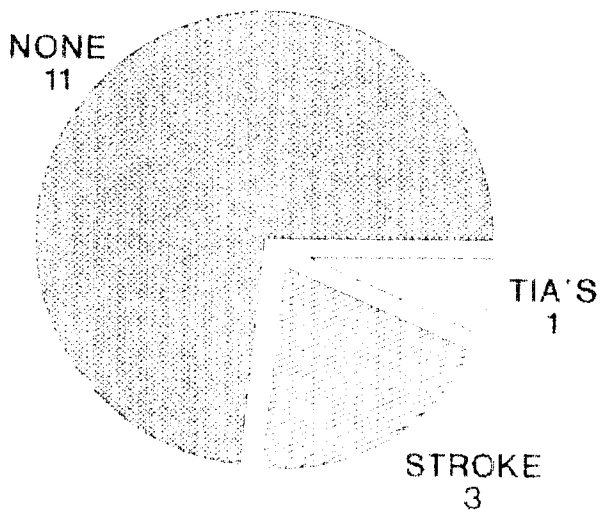
The most common neurological complication was a stroke, resulting in either a dense hemiplegia (6 cases) or a less severe upper motor neuron 7th nerve palsy (one case). The hemiplegias were occasionally associated with other neurological deficits, eg. aphasia. The cause of the stroke was established in four cases - intracerebral hematoma (from mycotic aneurysms) in three, and a brain abscess in one.

Two patients developed seizures. In one this was the presenting symptom of the endocarditis, and seizures did not recur once therapy for the endocarditis had been instituted. Computerized axial tomography (CAT-scan) in this

INFLUENCE OF VEGETATIONS ON NEUROLOGICAL EVENTS



VEGETATIONS



NO VEGETATIONS

FIGURE 7

case demonstrated a number of brain infarcts (possibly embolic from the endocarditis). Cerebral angiography was normal.

The second case of seizures occurred well after therapy had been commenced. At one stage status seizures occurred. CAT-scan in this case was normal, and futher investigations were not pursued.

Two cases of transient ischemic attacks were documented. Both consisted of transient hemiplegias. Once therapy for the endocarditis had been commenced, the symptoms did not recur.

In only two of the cases investigated were mycotic aneurysms found. The aneurysms were clipped in one, and were inaccessible in the other.

Blood cultures were positive in 5 of the 12 cases, which is slightly higher than the overall culture positivity rate but of no significance ($p<0,603$).

The echocardiographic findings and relevant clinical details of the patients who developed significant neurological sequelae are presented in figure 7. As is seen, there is no increased incidence of complications in those patients who had vegetations detected echocardiographically. Significant

complications occurred in 8 patients with vegetations (17%), and in four (27%) patients without definite vegetations ($p<0,304$). Echocardiographic absence of vegetations does therefore not protect against neurological complications occurring.

Futhermore the incidence of complications was as frequent with mitral valves (4 patients) as oppposed to aortic valves (5 patients). However, there were 3 patients who had double valve (aortic and mitral) involvement, whereas there were only 6 patients (9%) in the entire study of 63 patients who had double valve involvement ($p<0,078$).

ARTERIAL EMBOLIC COMPLICATIONS EXCLUDING NEUROLOGICAL COMPLICATIONS

The characteristics of patients with embolic complications excluding neurological complications are listed in appendix 4, and the incidence of complications in patients with and without vegetations in figure 8. Embolic complications occurred in 12 patients. The most common manifestation was an absent dorsalis pedis pulse, occurring in 7 patients. More ominous embolic complications occurred in 2 patients - brachial and popliteal arterial occlusions.

Neurological complications occurred in 2 patients who had other arterial embolic manifestations (peripheral pulse

EMBOLIC COMPLICATIONS AND PRESENCE OF VEGETATIONS

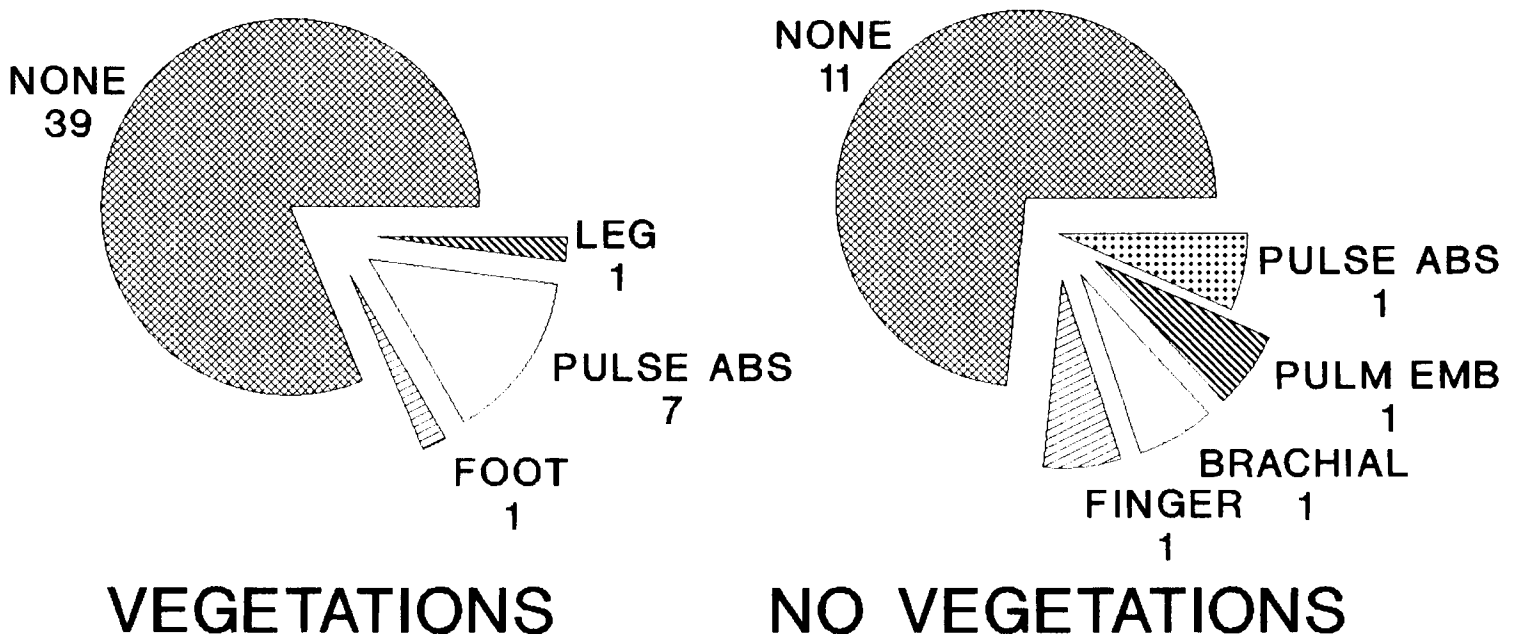


FIGURE 8

NEURO-EMBOLIC COMPLICATIONS AND PRESENCE OF VEGETATIONS

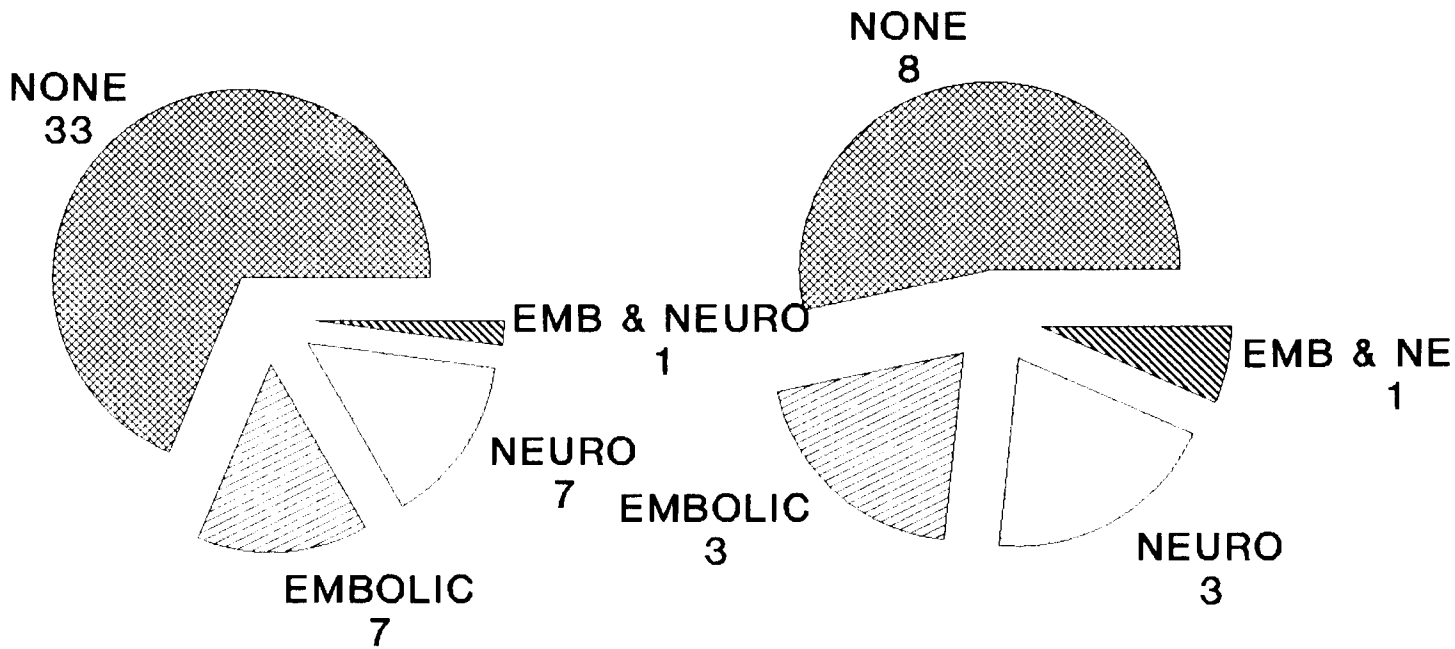


FIGURE 9

occlusions). Figure 9 combines the neurological and embolic complications in patients with and without vegetations. Assuming the neurological complications have an embolic origin, then patients without vegetations detected echocardiographically have a higher, but not statistically significant, incidence of embolic complications ($p<0,216$).

FOLLOW-UP OF VEGETATIONS AFTER MEDICAL THERAPY

Follow up data for at least six weeks on patients with vegetations after antibiotic therapy who did not require surgery is available on 12 patients. The patient with Q-fever in whom the vegetation was not detected two months after commencing therapy and subsequently returned on relapse a few months later has been mentioned (page 25). In a futher 5 patients who eventually underwent valve replacement, the vegetations were still detectable 3 to 8 months later prior to surgery. The echocardiographic description in these cases was that of a "healed" vegetation - more echo-dense than an "acute" vegetation, but at best still a subjective description. This was consistent with the surgical findings of a fibrosed sterile vegetation on the involved valve.

One patient has vegetations detectable 12 months after completing therapy, whereas two patients have vegetations some three months later. Only in two patients have

vegetations become undetectable - both within two months of antibiotic therapy.

In summary, in the 12 patients available for follow-up study of their vegetations, the vegetations were still detected echocardiographically in 8 (follow-up 3 months to a year), and were undetectable in 4 (undetectable within 2 months).

CORRELATION ECHO AND SURGICAL FINDINGS

Appendix 5 correlates the preoperative echocardiographic with surgical findings in patients who underwent valve replacement. Echocardiography underestimated the extent of vegetations in 14 cases. This investigation was particularly poor in detecting vegetations on the left atrial wall, papillary muscles and chords of the mitral valve. In the cases where the echocardiographic assessment underestimated the extent of involvement, the mitral and aortic valves were involved with equal frequency. When the mitral valve was involved, the vegetations were often on the posterior leaflet.

In two cases where a vegetation was considered to be on the mitral valve, at surgery the vegetation was in fact present on the aortic valve and not mitral. Both patients nonetheless required double valve replacement.

Vegetations were completely missed echocardiographically in 3 patients (2 involving the aortic valve, 1 mitral), and suspected in two cases (one each mitral and aortic valve). In all cases at surgery large vegetations were found.

In one case a vegetation was detected echocardiographically which could not be found macroscopically at surgery. The diagnosis of endocarditis in this case was based on histological findings of the excised valve.

In 50% of the examinations the echocardiographic assessment correlated reasonably accurately with the surgical findings. In only the single case described above did the echocardiographic assessment overestimate the extent of involvement with vegetations.

In 6 patients a root or annular abscess was found at surgery. All 6 cases were missed by echocardiography, and there was in fact one false positive report where an echocardiographically suspected root abscess was not demonstrated at surgery.

ECHO NEGATIVE SURGICAL AND POST MORTEM FINDINGS

There were 15 patients without vegetations detectable echocardiographically. Post mortem examinations were performed in two of these, and surgical valve replacement in seven. In both post mortem cases large vegetations were found on the mitral valves, with extensive endocarditis being present. In five of the seven patients who underwent valve replacement, macroscopic, and in three cases large, vegetations were found in five cases - on the aortic valve in three and mitral in two.

HISTOLOGY

Histological specimens were available for study in 33 patients (out of a total of 40 possible specimens - in five no specimen reached the pathology department; in one the non-infected valve was submitted; and in one the specimen was submitted for culture but not histology) (appendix 6).

For a definite diagnosis of infective endocarditis, the histological demonstration of bacterial colonies in valve tissue is required. This finding was present in 6 of the 33 histological specimens obtained. Features of acute endocarditis, viz. an acute inflammatory infiltrate with vegetations was demonstrated in 10 patients. A chronic

inflammatory response, with or without vegetations and compatible with subacute endocarditis (or partially treated acute endocarditis) was seen in 12 patients. In the remaining 5 patients there were no features of an inflammatory response.

The duration of antibiotic therapy prior to surgery and therefore histological examination of the valve is shown in table 13. In 4 of the 6 patients in whom organisms were demonstrated, antibiotic therapy had been given for over three weeks. Conversely, subacute histological changes were seen in 8 patients who were either undiagnosed at the time of surgery (2) or had received less than 2 weeks antibiotic cover. As expected, patients who had lost all histological evidence of an inflammatory response had been completed 6 weeks of therapy a few months prior to surgery.

In the 6 patients who were found to have bacterial colonies on their excised valves, 5 had echocardiographically demonstrated vegetations. Acute inflammatory changes were found in five patients with echocardiographic vegetations and 5 without.

Of the 40 patients who underwent surgery, 35 specimens were submitted for tissue culture. In only 3 cases was a positive culture obtained, and in only one of these was an organism positively identified. The three patients had been on

antibiotic therapy for a time period ranging from 2 to 6 weeks.

HISTOLOGICAL	DURATION OF ANTIBIOTIC THERAPY				
FINDINGS	< 2WEEKS	3-5WEEKS	6 WEEKS	>6 WEEKS	TOTAL
ORGANISMs	2	1	2	1	6 (5)
Acute	1	2	6	1	10 (5)
Subacute	(2)+6	2	2	0	12 (12)
No evidence	0	1	0	4	5 (5)

TABLE 13

Histological Findings and Duration of Antibiotic Therapy

(In parentheses under the total column is indicated the number of cases with echocardiographically detected vegetations).

DISCUSSION

TOTAL GROUP

Within a 22 month period, a total of 63 cases of infective endocarditis were prospectively identified and studied. It can be stated with reasonable confidence that this is the total Groote Schuur hospital experience with this condition during this period of time. This excluded patients with prosthetic valve endocarditis. The incidence of intravenous drug abuse in the population studied is very low, and no cases of endocarditis related to intravenous drug abuse were found. This contrasts with many previous studies which include prosthetic valve endocarditis, and right-sided endocarditis due to intravenous drug abuse[6,7,10]. Despite these exclusions, the number of cases of infective endocarditis at Groote Schuur hospital is surprisingly high - almost three per month. Compare this to the classic study of Pelletier and Petersdorf spanning a ten year retrospective period including cases at the three University of Washington hospitals where 125 cases were studied (4 cases/hospital/year)[15].

DIAGNOSTIC IMPLICATIONS

Previous reports vary as to the sensitivity of the echocardiographic detection of vegetations in patients with infective endocarditis, ranging from 40% to 80%[3,5-10]. We found echocardiography an extremely valuable tool in this regard, having a sensitivity of 76%. Of almost equal importance is the specificity of this test, being 95% in patients with suspected infective endocarditis. The specificity is obviously influenced by the type of patient referral, and would be high when the incidence of the disease in the patient population is low, but considering that more than 1 in 5 referrals in fact had infective endocarditis, this specificity is of diagnostic value. Previous studies with 2-D echocardiography have not determined the specificity of this investigation in patients with suspected infective endocarditis. With M-mode echocardiography a specificity of 96% has been reported[12].

The appearance of a vegetation can be simulated by conditions other than infective endocarditis[17],. The most common cause of false positive results, ie detection of vegetations in patients who did not have infective endocarditis, was flail mitral valve leaflets. This was found to be present in three patients who in fact came to surgery for severe mitral regurgitation. In all three, vegetations had been detected just before surgery was

undertaken, and although therapy for endocarditis had been initiated, no evidence to support this diagnosis was found on histological examination, and no vegetations were found at surgery. The prolapsing mitral valve due to a ruptured chord probably accounted for the echocardiographic findings. This error is of little importance in the patient operated on for heart failure but could be important if a false positive led to an inappropriate operation in a patient with some other febrile illness.

Acute rheumatic fever is sometimes difficult to differentiate from infective endocarditis. Six patients were in fact treated for infective endocarditis, but retrospectively it is more likely that they had acute rheumatic fever. Three of these patients required valve replacement and histological findings supported the diagnosis of acute rheumatic fever - two had had vegetations detected echocardiographically prior to surgery, as alluded to above.

GENERAL FEATURES

The mean age of the patients in this study was 37 years, which is considerably younger than the 54 years reported in other studies[10,18-20].

The most common underlying cardiac lesion in our patients was chronic rheumatic heart disease (52%), which is similar to earlier reviews[20,21], but higher than more recent reports (18%)[10,22]. This reflects the high incidence of rheumatic fever in our population group.

Intravenous drug abuse with subsequent right sided endocarditis is most uncommon in our population, which accounts for the comparatively low incidence of tricuspid endocarditis in this study.

Mitral valve prolapse was found in 11% of cases, which is almost identical to that of more recent studies undertaken since this condition was described[23], although some recent reports place the incidence as high as 29%[22]. In 30% of cases the native valve was thought to be normal prior to the endocarditis, in keeping with the reported incidence of 16-40% in most previous studies[10,15,18-22]. In one patient with mitral valve involvement with Hemophillus parainfluenza, no murmur was detectable initially, but appeared 10 days after initiation of therapy. This absence of murmurs in infective

endocarditis has been noted in as many as 15% of cases[19], mostly occurring with acute Staphyllococcal endocarditis and right-sided involvement

A precipitating factor could only be established in the minority of cases. Earlier reviews have emphasized the presence of precipitating factors[15], including recent dental procedures, but a few have also been unable to demonstrate the importance of such factors[19].

REFERRED PATIENTS

Being a referral centre, a substantial proportion of the cases identified had been referred from other centres (Tables 2 & 3). This unfortunately introduces an unavoidable element of bias into the results of the study. A second major drawback of this study in this regard is the absence of information on patients with infective endocarditis that were not referred from the outlying hospitals. The patients referred are a select group as most were referred for surgical intervention either during the acute phase of the illness or for valve replacement after receiving medical therapy but having deteriorated hemodynamically. There may have been many critically ill patients who died prior to transfer thus making the referred group mortality artificially low. Patients who remained stable on medical therapy would also not require referral, whereas the

majority of patients referred subsequently underwent valve replacement - thus the incidence of surgery in the total group is falsely elevated.

Table 3 (page 25) depicts the differences with statistical evaluation of all the major variables between patients referred from outlying centres and the "original" Groote Schuur Hospital patients. The two variables which show a significant difference are the incidence of positive blood cultures, and (as mentioned) the clinical outcome as regards surgical intervention and mortality.

Right-sided endocarditis has a relatively good prognosis[24,42], and this may account for the fact that no case of right-sided involvement in the referred patients was seen. Patients with this form of endocarditis less frequently require valve replacement. Furthermore intravenous drug abuse is comparatively infrequently seen in our population - this form of drug abuse being the major precipitating factor of right-sided endocarditis in some other countries.

The reasons for the low blood culture positivity rate in referred patients is unclear. Less sophisticated laboratory facilities and back-up is available in the periphery as compared to Groote Schuur hospital which is an academic institution. There is also no information available on the

incidence of positive cultures in the patients that were not referred, making it difficult to comment on the overall positivity rate. Staphyllococcus aureus was not isolated in the referred patients - this form of left-sided endocarditis has a notorious prognosis. Furthermore, Streptococcus viridans was less frequently cultured from referred patients. This presumably reflects prior antibiotic therapy and successful elimination from the blood of this usually sensitive organism.

There was no statistical difference in the incidence of echocardiographically detected vegetations between referred patients and those from Groote Schuur. However, in the referred group of patients, vegetations were detected echocardiographically more frequently in patients with negative blood cultures (Table 15). This difference is statistically significant ($p<0.05$). This suggests that in the outlying centres blood cultures and echocardiography complement each other in the investigation of patients with suspected infective endocarditis. However no firm conclusion can be drawn as to the superiority of one investigation over the other as the information on all patients with infective endocarditis from the outlying hospitals is not available.

The breakdown of blood cultures and echocardiographic findings in the Groote Schuur patients is not as striking

(table 16), but does show that very few patients are both culture negative and have no detectable vegetations on their valves. This supports the conclusion that blood cultures and echocardiography complement each other in the investigation of patients with suspected infective endocarditis.

TABLE 15

BLOOD CULTURES AND THE PRESENCE OF VEGETATIONS IN REFERRED PATIENTS

		Echocardiographic Vegetations		
		Positive	Negative	Total
Blood Cultures	Positive	2	3	5
	Negative	17	1	18
	Total	19	4	23

TABLE 16

BLOOD CULTURES AND THE PRESENCE OF VEGETATIONS IN GROOTE SCHUUR PATIENTS

		Echocardiographic Vegetations		
		Positive	Negative	Total
Blood Cultures	Positive	12	8	20
	Negative	15	3	18
	Total	27	11	38

The underlying valve pathology was similar in patients referred to Groote Schuur, and in patients presenting directly to Groote Schuur. Finally, aortic valve endocarditis was more frequent in referred patients. This may be due to the more aggressive nature of aortic valve (as opposed to mitral or right-sided) involvement[6,12], and is discussed more fully later.

Because of concern that patient characteristics and selection of patients for referral could influence results, the analysis of sensitivity and specificity of the echocardiographic results were separately performed. These results are presented in table 3 (page 25). As can be seen, the results are not significantly influenced.

BLOOD CULTURES

Previous studies quote a positive blood culture rate in excess of 80%[5,6,15]. This at first seems discrepant from this study (41%), but in many studies a positive blood culture is a prerequisite for the diagnosis of endocarditis[6,8,25]. The diagnosis in this study was more often established on histological criteria, which obviated the need for clinical (including a blood culture) criteria

to establish a diagnosis.

As a diagnostic investigation, echocardiography is thus more sensitive than blood cultures : 78% vs 41% (or 73% vs 53% if referred patients are excluded). Perhaps the detection of a vegetation on echocardiography should supplant a positive blood culture as a criterion for the diagnosis of infective endocarditis (especially in outlying centres).

Remarkably, although the overall blood culture positivity rate was 53% in the Groote Schuur patients (and 22% in the referred group), in patients without vegetations the blood culture was positive in 73% (in referred patients 75%).

Conversely, in the Groote Schuur patients with negative blood cultures, vegetations were detected in 15/18 (83%) cases (table 16, page 56), as opposed to 12/20 (60%) with positive blood cultures ($p<0,05$). This is even more striking in the referred group of patients - 94% and 40% respectively.

The majority of patients in echocardiographic studies of infective endocarditis are culture positive - this being an inclusion criterion for entry into the study. Thus echocardiographic features in culture negative endocarditis has been inadequately documented. Rubenson et al in their 11 cases of culture negative endocarditis found

echocardiographically (M-mode and 2-dimensional) detected vegetations in 8 (73%) cases - but evidence of infective endocarditis in ALL patients examined by 2-dimensional echocardiography[26]. Our findings impressively demonstrate the usefulness of echocardiography in diagnosing culture negative endocarditis.

These two investigations (blood cultures and vegetations) therefore complement each other diagnostically. In only 4 cases were both investigations negative in patients with infective endocarditis.

The organisms responsible for the endocarditis are similar to other reported series, with Streptococci being the most common isolate (52%) followed by Staphyllococci (20%)[10,18-21,25]. The poor prognosis of patients with Staphyllococcus aureus endocarditis was confirmed in our series. Only two of the five cases survived, both requiring valve replacement. **Urgent surgery should be seriously considered when this organism is responsible for the endocarditis[27].**

VALVE LOCATION

In previous studies of right-sided infective endocarditis, Staphylococcus aureus is more frequently cultured, the prognosis is generally good, the underlying heart valve is normal and intravenous drug abuse is often a precipitating

factor[24]. Our four cases differed from these findings :- Staphyllococcus was cultured in one patient (but all four had positive blood cultures), two required surgery but none died, one patient had a congenital ventricular septal defect but the other three had normal underlying hearts, none of the patients abused intravenous drugs.

Left sided endocarditis predominated, and the reasons for this have been referred to. Vegetations were more likely to be absent when the mitral valve was involved, ie echocardiographic vegetation negative mitral valve endocarditis was more frequent than aortic valve endocarditis. The reason for this remains unclear. Speculation would suggest that interrogation of the mitral valve is more difficult - difficult to detect vegetations on the chordae and subvalvar apparatus. In contrast, examination of the aortic valve is relatively easy.

PROGNOSTIC IMPLICATIONS : OUTCOME

MORTALITY

The mortality rate of 24% in this study is similar to that reported in recent surveys[10,27,28] - although these included patients with prosthetic valve endocarditis and in this subset the mortality rate was often substantially higher (53%). The mortality in the referred group of patients was substantially lower (9%) than in the Groote Schuur patients (32,5%)

Mean age was not found to be an adverse prognostic factor, but the mortality rate in the subgroup of patients over 60 years old was 62,5% [10]. The major cause of death was hemodynamic deterioration[15,27].

Mortality rate in Groote Schuur patients in whom no vegetations were detected echocardiographically is higher than in patients with vegetations (45% and 28% respectively), although this difference is not statistically significant ($p<0,254$). This is in sharp contrast to other studies[6,8,10,12] in which patients with vegetations had a much higher mortality rate. A few reports are in agreement and have also found no increased mortality rate in patients with vegetations detected echocardiographically[9,27,], but almost no studies have

shown the trend demonstrated here with an increased mortality in patients without vegetations..

SURGERY

The presence of a vegetation in this study did not result in surgery being required more often than in patients without echocardiographically detected vegetations. This is in keeping with the conclusions of some investigators[3,9], but the majority would disagree[8,12,13,27]. Most observers agree that the presence of a vegetation per se should not be regarded as an indication for surgery[3,7-9]. Most of the patients referred from outlying centres were referred exclusively for surgical assessment, and vegetations were detected in 83% of these patients. Analysis of the Groote Schuur patients on their own demonstrates that 55% of patients with vegetations underwent surgery, and only 18% of patients without vegetations had surgery.

Hemodynamic deterioration is the most frequent indication for surgical intervention[28,30,31]. Apart from the 3 patients who refused surgery (and died), in retrospect death could have been avoided by earlier surgical intervention in at least one other patient. Surgery can be safely performed in patients with acute infective endocarditis[28,31,32], and there was only one death directly related to the surgical procedure, despite the fact that in 17 patients surgery was

performed either urgently or before completion of medical therapy. Although each case should be individualized, the results of this study support the contention that surgery should not be refused in an acutely ill patient with endocarditis, on the grounds of a high surgical mortality, and in fact may be life-saving[31,32].

It is noteworthy that patients who have a shorter duration of symptoms (7 days) prior to diagnosis of infective endocarditis, tended to survive without requiring surgical intervention. Patients who underwent surgery had an average symptom duration prior to diagnosis of 64 days, with those dying an intermediary 21 days. This may mean that prompt diagnosis and institution of appropriate therapy reduces intracardiac damage. Skehan et al in their paper on mortality in infective endocarditis found that patients with a shorter symptom duration fared less well and had an increased mortality[10].

Furthermore, in patients who survived and did not require surgery, the mitral valve was more frequently involved than the aortic (7 vs 1), whereas the tricuspid valve was involved in two cases, and both aortic and mitral in one. The relevance of this finding is again unclear. Possibly the natural history of aortic regurgitation (which may be relatively acute in endocarditis) is more aggressive than mitral regurgitation. Moreover, these findings are supported

by the autopsy series of Buchbinder and Roberts who demonstrated that significantly fewer patients with mitral valve vegetations as opposed to aortic valve vegetations had disruption of the involved valve[33]. Dinuble in his review of surgery in active endocarditis states that aortic valve involvement is more serious than mitral valve infection in both frequency and severity of cardiac decompensation[30]. However Lerner et al[19] suggest this observation may be due to confounding factors - viz mitral involvement occurs in the young female with rheumatic heart disease, and aortic involvement due to calcific degeneration in the elderly male. Age[10,20,], sex, and underlying valve pathology[19] may all influence prognosis. Other echocardiographic studies of vegetations in endocarditis have also noted a worse prognosis with aortic valve involvement6,12.

In general, in the Groote Schuur patients (patients from outlying centres are excluded as they form a very select group of patients referred almost exclusively for surgery) the following conclusions may be made :-

1) Patients who survived, required surgery less often if no vegetations were detected echocardiographically.
2) Paradoxically, patients without vegetations demonstrated echocardiographically had a higher mortality (45% vs 28%). These differences do not reach statistical significance. The absence of vegetations may induce complacency in the

clinician, leading him to defer necessary and possibly life-saving surgery.

3) Surgery was performed more frequently in patients with echocardiographic vegetations. Vegetations per se were not an indication for surgery.

RENAL FUNCTION

In patients with renal impairment Vegetations were NOT detected on echocardiography in 3 (20% of patients without vegetations had renal impairment), and present in 12 (25% of patients with vegetations; $p<0,50$). As the number of patients with renal impairment overall is relatively small, it is difficult to detect any statistical association between the presence of a vegetation and renal impairment. In this study no such association is evident. In the patients with renal impairment there was a modest improvement after treatment of the endocarditis, which for all these particular patients happened to include valve replacement, as depicted in table 8.

In only one patient was renal biopsy performed. Once the diagnosis of infective endocarditis is established renal biopsy adds little further information and may merely confirm that renal impairment is due to a glomerulonephritis resulting from the endocarditis. Most studies of

glomerulonephritis in infective endocarditis are biased towards the severely ill patients, with histology obtained at autopsy[34]. The actual incidence of focal and diffuse glomerulonephritis occurring in the course of endocarditis has therefore not been established. Renal functional impairment as a consequence of the glomerulonephritis is uncommon[35].

Furthermore, the cause of renal impairment in patients with infective endocarditis is multifactorial. Contributing factors include the underlying infection and sepsis, glomerulonephritis, acute tubular necrosis aggravated by volume depletion, and antibiotic therapy (aminoglycosides). Thus "renal impairment" in this setting should be regarded with caution.

In all patients with significant renal impairment there was evidence of an immune complex glomerulonephritis as evidenced by depressed levels of serum complement, hematuria and casts on urine microscopy.

Notably, all patients with renal impairment either died or required valve replacement.

NEUROLOGICAL COMPLICATIONS

Neurological complications occurred in 19% of patients. In the series of Pruit et al, the incidence of neurological complications was 39%, but only 12% once patients that had been referred from other centres were excluded[36].

Neurological complications occurred in 17% of patients with vegetations and 27% of patients without ($p<0,31$). Paradoxically this indicates that neurological complications tended to occur more frequently in patients without detectable vegetations.

Although the specific valve (mitral or aortic) did not by themselves predict subsequent neurological involvement, of interest is that 3 patients with neurological manifestations had double valve (aortic and mitral) involvement, whereas there were only 6 patients (9%) in the entire study of 63 patients who had double valve involvement. Of all factors considered, double valve involvement seems to be the only predictor of neurological complications occurring. Logically the more extensive the vegetations the more likely it is that an embolic episode will occur. However, Pruit et al in their retrospective study of 218 patients over a ten year period found that mitral valve involvement predisposed to neurological

complications (as opposed to aortic and double valve involvement)36.

ARTERIAL EMBOLI

As the overall number of embolic events is small, if we combine the embolic and neurological events, assuming the neurological complications have an embolic origin, then the surprising finding is that patients without vegetations detected echocardiographically have a higher incidence of embolic complications, but this is not statistically significant ($p<0,60$) (figure 9). Patients without vegetations are therefore not immune to embolic complications from infective endocarditis. Previous studies have demonstrated either no increase[9], or a definite increase[5,7,8,27] of embolic complications in patients with demonstrable vegetations. The possibility exists that such "embolic" complications are not truly embolic but may be immune-complex mediated.

Another explanation for the observation that embolic phenomena occur in the absence of a detectable vegetation is that the embolic complication occurred as a result of dislodgement of the vegetation which therefore is no longer detectable. This has previously been demonstrated[5,6,37]. As most embolic events occurred on presentation, this suggestion is plausible. Other studies have demonstrated

embolic events occurring in up to 30% of patients with vegetations[5,7,8]. In our group, the incidence of embolic events is substantially lower, and paradoxically higher in patients without vegetations. Also, the embolic events in our series occurred early in the course of the disease, as opposed to the findings of Stewart et al[7], where some complications occurred after completion of therapy.

SERIAL FOLLOW UP OF VEGETATIONS

In this study, serial follow-up of vegetations was of little diagnostic or prognostic value. The vegetations that became undetectable subsequently did so within two months of presentation. Other vegetations are still present a year after therapy, the patients remaining well. Vegetations that remain present echocardiographically and were removed after a prolonged period during valve replacement were sterile and consisted of fibrous tissue, with no evidence of acute inflammatory changes. Echocardiographically the vegetations tended to become more echodense, but these changes are subjective and depend heavily on the echocardiographer's interpretation. The accuracy of descriptions such as "more echodense than before" is debatable. In accordance with other investigators5,7 we feel echocardiography is of little help in assessing activity of the disease process once therapy has been instituted and that serial follow-up of vegetations is of little clinical assistance. A few

investigators suggest there may be some value in following up vegetation size[37], and density[1].

Relapse of the endocarditis is usually heralded by other clinical manifestations, and echocardiography presumably would be insensitive in this regard. However, mention has been made of the patient with Q-fever endocarditis in whom the vegetations recurred with his relapse. Unfortunately he presented late with his relapse, and the value of echocardiography in this case is speculative.

CORRELATION OF ECHO AND SURGICAL FINDINGS

Echocardiographic findings in patients with infective endocarditis generally correlate reasonably well with surgical findings[5]. In 50% of our examinations the echocardiographic assessment correlated accurately with the surgical findings. In only the single case described did the echocardiographic assessment overestimate the extent of involvement with vegetations.

However in a large proportion of patients, although echocardiography correctly detected the presence of vegetations, it grossly underestimated the involvement of underlying structures - especially when the left atrial wall or papillary muscles or chordae were involved. Martin et al in their study found that echocardiography overestimated the extent of involvement[3].

There are case reports of echocardiography detecting mitral ring and aortic root abscesses[38-40], but the sensitivity of echocardiography in this respect remains to be established. In this series, echocardiography was particularly poor at delineating root and annular abscesses. All 6 cases were missed by echocardiography, and there was in fact one false positive report. Pringle et al also found that echocardiography was unhelpful in detecting abscesses[14]. John et al in their abstract found echocardiography

correctly identified the presence of an aortic root abscess at surgery in 6 of 49 (23%) patients who had a root abscess[41]. Our results are not as good.

In general, when echocardiography detected vegetations, the extent of involvement was greater than the echocardiographic assessment.

ECHO NEGATIVE SURGICAL AND POST MORTEM FINDINGS

The most instructive aspect of this study is the cases in whom echocardiography failed to detect a vegetation, but subsequently were demonstrated at surgery or post-mortem. There were 9 cases where echocardiographic vegetations were not detected, and either surgery (7) or post-mortem (2) was performed.

The site of the involved valve does not influence the inaccuracy of echocardiography in detecting vegetations, as in these cases the mitral and aortic valve were equally involved. Furthermore, 5 of the 7 surgical cases underwent operation more than three weeks after the diagnosis had been made, and one of the patients who came to post mortem had died after six weeks of therapy. This disputes the theory that acute "fresh" vegetations that have not had time to organize may be missed on echocardiography, as these cases cannot be considered to have "acute" vegetations.

Vegetations that were missed echocardiographically were often found to be extensive. The valve involved was completely destroyed by vegetations in four of these cases. In these the vegetations were possibly less mobile and attached closer to the valve annulus. This may partially explain the difficulty of detecting them on echocardiography. Other studies have also found vegetations at surgery when echocardiography failed to detect them preoperatively[14].

Of paramount importance is that in only two of the nine cases where echocardiography failed to detect vegetations were there no vegetations found macroscopically. Diagnosis in these cases was based on histology. This finding suggests that in most patients with endocarditis there are in fact vegetations present, and the true pathological absence of vegetations in patients with infective endocarditis is in fact quite rare. In only four of the 44 cases where either a histological specimen or post mortem examination was performed, were there in fact no vegetations to be found macroscopically. Two of these cases have been alluded to above. In the third surgery was performed six months after therapy for endocarditis, and although the preoperative echocardiographic examination referred to a vegetation (healed), no vegetation was found. In the fourth case a vegetation that had been described echocardiographically

could not be found at surgery. Again this diagnosis was based on histological criteria. Buchbinder and Roberts in their study of forty-five necropsy patients make no mention of vegetations being absent, and in all patients the site of vegetations was demonstrated[33]. The exact incidence of small vegetations that are too small to be detected echocardiographically (thought to be less than 2mm[1]) in patients with infective endocarditis remains to be established. From our findings this incidence must be very low, and for practical purposes the vast majority of patients with infective endocarditis will have vegetations of sufficient size that they should be detectable echocardiographically.

In conclusion, only three of 43 patients where specimens were obtained had infective endocarditis without macroscopic vegetations. This finding places doubt on the whole concept of "vegetation negative" endocarditis as described by echocardiographic findings. This also easily explains the similarity in complication rate and clinical course in patients with and without detectable vegetations, and makes the distinction between echocardiographic vegetation positive and negative infective endocarditis irrelevant.

HISTOLOGY

There is no clear relation between the histological findings of acute endocarditis (bacterial colonies and inflammatory response) and duration of antibiotic therapy the patient received prior to surgical removal of the infected valve. As shown, gram positive organisms were demonstrated in some patients who had received up to 6 weeks antibiotic therapy. Acute inflammatory changes tended to be more frequently found after 6 weeks of antibiotic therapy than in the acute phase, whereas subacute and a more chronic inflammatory response was found in the earlier stages of the infection. The reason for these findings remain unclear, and any explanation at this stage would be speculative. The only correlation that appears logical is that evidence of an inflammatory response was not evident in most patients who had completed antibiotic therapy and only required surgery some time later - presumably the natural history of hemodynamic deterioration in a damaged valve.

CONCLUSION

Several important and clinically useful conclusions can be drawn from this prospective review of 275 patients referred for echocardiography for investigation of suspected infective endocarditis :-

1) The presence of a vegetation detected echocardiographically in patients with suspected infective endocarditis is of diagnostic significance. In patients presenting directly to Groote Schuur hospital, ie excluding all patients referred from other centres, the finding of a vegetation has a sensitivity of 73%, and a specificity of 95%, in the diagnosis of infective endocarditis.

Blood cultures were positive in only 53% of Groote Schuur patients (41% in all cases). At Groote Schuur hospital echocardiography is a superior diagnostic investigation.

In patients without vegetations detected echocardiographically, blood cultures are frequently positive (73%). The reason for this anomaly remains unclear. Conversely in patients with negative blood cultures, vegetations were detected in 83%.

2) In the Groote Schuur patients, the presence of a vegetation detected by echocardiography is not indicative of an unfavorable outcome.

3) Embolic complications and renal impairment did not occur more commonly in those with vegetations.

4) Echocardiography is reasonably accurate (50% of cases) in assessing the extent of vegetations as determined at post mortem and surgery. In most of the remaining cases the extent of involvement is underestimated by the echocardiographic examination. Aortic root abscesses were usually missed.

5) The only probable predictor of neurological complications is simultaneous involvement of mitral and aortic valves - neurological problems occurred in 50% of patients with this combination. The number of patients with double valve involvement is small, thus no statistical significance was obtained.

6) All patients with renal impairment either required valve replacement or died.

7) The vast majority of cases of infective endocarditis have vegetations physically present on the valves. The reasons for these vegetations not being detectable echocardiographically remain unclear. The echocardiographic absence of a vegetation is of absolutely no prognostic significance. In this study, only 3 of 43 were truly vegetation negative as determined at surgery or post mortem.

REFERENCES

1) Dillon JC, Feigenbaum H, Konecke LL, Davis RH, Chang S. Echocardiographic manifestations of valvular vegetations. Amer Heart J 1973;86:698-704.

2) Gilbert BW, Robyn S, Haney RN, Crawford F, McClellan J, Gallis HA, Johnson M, Kisslo JA. Two dimensional echocardiographic assessment of vegetative endocarditis. Circulation 1977;55:346-53.

3) Martin RP, Meltzer RS, Stinson EB, Rakowski H, Popp RL. Clinical utility of two dimensional echocardiography in infective endocarditis. Amer Journ Card 1980;46:379-385.

4) Mintz GS, Kotler MN, Segal BL, Parry WR. Comparison of two-dimensional and M-mode echocardiography in the evaluation of patients with endocarditis. Am J Cardiol 1979;43:738

5) Roy P, Tajik AJ, Giuliana ER, Schattenberg TT, Gau GT, Frye RL. Spectrum of echocardiographic findings in bacterial endocarditis. Circulation 1976;53:474-482.

6) Buda AJ, Zotz RJ, LeMire MS, Bach DS. Prognostic significance of vegetations detected by two-dimensional echocardiography in infective endocarditis. Am Heart J 1986;172:1291-1296.

7) Stewart JA, Silimperi D, Harris P, Wise NK, Fraker TD, Kisslo JA. Echocardiographic documentation of

vegetative lesions in infective endocarditis: Clinical implications. Circulation 1980;61:374-380.

8) O'Brien JT, Geiser EA. Infective endocarditis and echocardiography. A Heart J 1984;108:386-394.

9) Lutas EM, Roberts RB, Devereux RB, Prieto LM. Relation between the presence of echocardiographic vegetations and the complication rate in infective endocarditis. Am Heart J 1986;112:107-113.

10) Skehan JD, Murray M, Mills PG. Infective endocarditis: incidence and mortality in the North East Thames Region. Br Heart J 1988;59:62-8.

11) Hickey AJ, Wolfers J, Wilcken DEL. Reliability and clinical relevance of detection of vegetations by echocardiography in bacterial endocarditis. Br Heart J 1981;46:624-8.

12) Come PC, Isaacs RE, Rilley MF, Diagnostic accuracy of M-mode echocardiography in active infective endocarditis and prognostic implications of ultrasound-detectable vegetations. AHJ 1982;103:839-847.

13) Sutton. Echocardiography in infective endocarditis. B Heart J 1976;38:312-

14) Pringle TH, Webb SW, Khan MM, O"Kane HOJ, Cleland J, Adgey AAJ. Clinical, echocardiographic, and operative findings in acute infective endocarditis. Br Heart J 1982;48:529-37.

15) Pelletier LL, Petersdorf RG. Infective endocarditis: A review of 125 cases from the University of Washington hospitals,1963-72. Medicine 1977;56:287-313.

16) van der Bel-Kahn JM, Watanakunakorn C, Menefee MG, Long HD, Dicter R. Chlamydia trachomatis endocarditis. AHJ 1978;95:627-636.

17) Amsterdam EA. Value and limitations of echocardiography in endocarditis. Cardiology 1984;71:229-231.l

18) von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. Ann Int Med 1981;94:505-518.

19) Lerner PI, Weinstein L. Infective endocarditis in the antibiotic era. NEJM 1966;274:199-206, 259-266, 323-331, 388-393.

20) Uwaydah MM, Weinberg AN. Bacterial endocarditis - a changing pattern. NEJM 1965;273:1231-1235.

21) Rabinovich S, Evans J, Smith IM, January LE. A long-term view of bacterial endocarditis 337 cases 1924 to 1963. Ann Int Med 1965;63:185-198.

22) McKinsey DS, Ratts TE, Bisno AL. Underlying cardiac lesions in adults with infective endocarditis. The changing s+spectrum. AJM 1987;82:681-688.

23) MacMahon SW, Roberts *JK, Kramer-Fox R, Zucker DM, Roberts RB, Devereux RB. Mitral valve prolapse and infective endocarditis. Am Heart J 1987;113:1291-1298.

24) Panidis IP, Kotler MN, Mintz GS, Segal BL, Ross JJ. Right heart endocarditis : Clinical and

echocardiographic features. Am Heart J 1984;107:759-764.

25) Werner AS, Cobbs CG, Kaye D, Hook EW. Studies on the bacteremia of bacterial endocarditis. JAMA 1967;202: 199-203.

26) Rubenson DS, Tucker CR, Stinson EB, London EJ, Oyer P, Moren-Cabral R, Popp RL. -The use of echocardiography in diagnosing culture negative endocarditis. Circulation 1981;64:641-646.

27) Varma MPS, McCluskey DR, Kahn MM, Cleland J, O'Kane HO, Adgey AAJ. Heart failure associated with infective endocarditis.A review of 40 cases. Br Heart J 1986;55: 191-7.

28) McAnulty JH, Rahimtoola SH. Surgery for infective endocarditis. JAMA 1979;242:77-79.

29) Davis RS, Strom JA, Frishman W, Becker R, Matsumoto M, LeJemtel TH, Sonnenblick EH, Frater RWM. The demonstration of vegetations by echocardiography in bacterial endocarditis. Amer J Med 1980;69:57-63.

30) Dinubile MJ. Surgery in active endocarditis. Ann Int Med 1982;96:650-659.

31) Croft CH, Woodward W, Elliot A, Commerford PJ, Barnard CN, Beck W. Analysis of surgical versus medical therapy in active complicated native valve infective endocarditis. Amer J Card 1983;51:1650-1655.

32) Wilson WR, Danielson GK, Giuliani ER, Washington JA, Jaumin PM, Geraci JE. Valve replacement in patients

with active infective endocarditis. Circulation 1978; 58: 585-588.

33) Buchbinder NA, Roberts WA. Left-sided valvular active infective endocarditis. A study of forty-five necropsy patients. Amer J Med 1972;53:20-35.

34) Feinstein EI, Eknoyan G, Lister BJ, Kim H, Greenberg SD. Renal complications in infective endocarditis. Am J Nephrol 1985;5:457-469.

35) Neugarten J, Baldwin DS. Glomerulonephritis in Bacterial endocarditis. AmJMed 1984;77:297-304

36) Pruit AA, Rubin RH, Karchmer AW, Duncan GW. N eurological complications of bacterial endocarditis. M edicine 1978;57:329-45.

37) Stafford A, Wann LS, Weyman AE, Feigenbaum H. Serial echocardiographic appearance of healing bacterial vegetations. AJCard 1979;44:754-760.

38) Scanlan JG, Seward JB, Tajik AJ. Valve ring abscess in infective endocarditis : Visualization with wide angle two dimensional echocardiography. Amer J Card 1982;49:1794-1800.

39) Nakamura K, Suzuki S, Satomi G, Hiyashi H, Wirosawa K. Detection of mitral ring abscess by two dimensional echocardiography. Circulation 1982;65:816-818.

40) Wong CM, Oldershaw P, Gibson DG. Echocardiographic demonstration of aortic root abscess after infective endocarditis. Br Heart J 1981:46:584-6.

41) John RM, Pugsley W, Treasure T, Sturridge MF, Swanton RH. Aortic root abscess complicating aortic valve endocarditis. Proc Br Cardiac Soc 93.

42) Tricuspid valve endocarditis. Amer Heart J 1989;17:1140-1146.

APPENDIX 1

CHARACTERISTICS OF ALL PATIENTS
WITH INFECTIVE ENDOCARDITIS

INITIALS	AGE	SEX	SYMP DUR	UNDERLY VALVE	CULTURE	VEGETAT	IND/SURG	TIME SUR FROM DIAG	VALVE involved	VALVE REPLACED	COMPLICATIONS
PROVEN IE : SURGERY											
1) CF	47	F	1 MONTH	MVP	Str vir	PROB	EMBOLI	3 WEEKS	MV	MV	VII PALSY; EMBOLUS RT FOOT
2) SJ	33	F	1 DAY	NORMAL	N. gon	PROB	CCF	5 DAYS	AV	AV	
3) VN	30	F	4 MONTHS	RHD	NEG	DEF	CCF	6 WEEKS	MV	MV	ABSENT RT
4) JN	18	F	6 WEEKS	RHD	NEG	DEF	INFECT	6 WEEKS	MV	MV	OSLER NODE FOOT
5) EP	35	M	6 MONTHS	NORMAL	NEG	DEF	CCF	11 DAYS	A&MV	A&MV	SEIZURE;DIALYSIS
6) HK	56	M	1 MONTH	RHD	NEG	DEF	CCF	6 WEEKS	AV	AV ABSC	EMBOLUS R
7) JS	70	M	3 WEEKS	NORMAL	Chlam	ABSENT	CCF	6 WEEKS	AV	AV	
8) JN	48	M	4 DAYS	NORMAL	NEG	DEF	CCF	19 DAYS	AV	AV	MYCOT AN;ABSENT RT DP
9) BK	48	M	8 MONTHS	RHD	NEG	DEF	CCF	6 WEEKS	AV	AV	RENAL IMP
10) DM	21	M	1 MONTH	L-TRANSP	NEG	PROB	CCF	6 WEEKS	AV	A&MV	
11) NJ	35	F	5 MONTHS	RHD	NEG	DEF	CCF	10 DAYS	A&MV	A&MV	ABS RT DP
12) KS	18	M	1 MONTH	RHD	NEG	DEF	CCF	14 DAYS	MV	MV	ABS DP LT
13) LB	47	F	3 DAYS	RHD	NEG	DEF	CCF	6 WEEKS	AV	A&MV	
14) DT	33	M	3 MONTHS	NORMAL	NEG	DEF	CCF	3 MONTHS	AV	AV,FIST-RV	
15) PJ	26	M	2 MONTHS	RHD	NEG	DEF	CCF	4 MONTHS	AV	AV	
16) DP	69	M	3 MONTHS	NORMAL	S.bovis	DEF	CCF	6 MONTHS	AV	AV	TIA'S
17) RJ	50	M	4 MONTHS	RHD	NEG	DEF	CCF	8 DAYS	AV	AV	DIALYSIS
18) LK	39	M	6 MONTHS	RHD	not done	DEF	CCF	NOT DIAG	AV	A&MV	
19) RdP	36	M	3 MONTHS	RHD	S.mitior	DEF	EMB	1 DAY	AV	A&MV	EMB RT LG
20) DP	57	M	3 MONTHS	MVP	NEG	DEF	CCF	3 WEEKS	MV	MV	RENAL IMP
21) MN	33	M	2 MONTHS	RHD	NEG	DEF	CCF	12 DAYS	MV	MV	RENAL IMP
22) SL	14	F	2 WEEKS	VSD	Str mill	DEF	VSD IE	3 WEEKS	TV,PV	PV	
23) BN	32	F	2 MONTHS	RHD	Strep	DEF	CCF	6 WEEKS	MV	MV	
24) YA	38	M	1 WEEK	NORMAL	NEG	DEF	CCF	23 DAYS	AV	AV	
25) TL	23	M	2 WEEKS	RHD	NEG	DEF	IE	2 MONTHS	AV	A&MV	
26) SG	13	M	2 WEEKS	SUBAOST	NEG	DEF	CCF	6 WEEKS	AV	AV	
27) BM	13	M	1 MONTH	RHD	NEG	DEF	CCF	4 MONTHS	MV&AV	M&AV	
28) AM	29	M	3 WEEKS	NORMAL	Staph au	DEF	IE	53 DAYS	PV	PV	
29) MH	27	M	3 WEEKS	RHD	NEG	DEF	CCF	13 DAYS	AV	A&MV ABS	DIALYSIS
30) MP	22	F	1 MONTH	RHD	a-h Strep	DEF	CCF	8 MONTHS	AV	AV	
31) EB	29	M	1 MONTH	NORMAL	NEG	DEF	CCF	13 DAYS	AV	AV	ABS DP RENAL IMP
32) RS	45	M	1 DAY	RHD	NEG	DEF	CCF	4 MONTHS	AV	AV	SEIZURES
33) DW	71	M	6 MONTHS	MVP	Coryneb	ABSENT	IE	30 DAYS	MV	MV	RENAL IMP
34) CJ	27	F	6 MONTHS	RHD	not done	DEF	CCF	NOT DIAG	AV	A&MV	
35) MK	14	M	3 MONTHS	COARC REP	NEG	DEF	CCF	6 WEEKS	AV	A&MV	
36) LD	30	F	3 WEEKS	NORMAL	Strep mit	DEF	CCF	6 WEEKS	MV	MV	
37) PH	43	F	1 DAY	RHD	Staph au	ABSENT	CCF	7 MONTHS	MV	MV	RENAL IMP; GANGRENE FINGER
	35	M25 F12	64 DAYS	RHD 20 NORMAL 10 CONG 4 MVP 3		DEF 31 PROB 3 ABSENT 3	CCF 30 IE 5 EMB 2				

PROBABLE IE : MEDICAL

	AGE	SEX	SYMP DUR	NATIVE	VALVE	CULTURE	VEGETAT	COMPLIC	DURATION F UP
1) RS	27	M	1 WEEK	?MVP	MV	H.pinfl	DEF		18 MONTHS
2) MS	26	F	ASYMPT	RHD	MV	NEG	DEF		1 YEAR
3) LF	17	M	1 DAY	RHD	AV	NEG	DEF	STROKE	6 MONTHS
4) MD	54	F	2 WEEKS	NORMAL	TV	Strep	DEF		3 MONTHS
5) CM	30	F	3 WEEKS	MVP	MV	NEG	ABSENT		9 MONTHS
6) LV	10	M	3 DAYS	RHD	MV&AV	a-hem Str	DEF	STROKE	1 YEAR
7) KJ	46	F	5 DAYS	MVP	MV	Staph epi	DEF		3 MONTHS
8) AD	32	F	1 DAY	RHD	MV	a-hem Str	ABSENT	ART OCCL (LT BRACH	3 MONTHS
9) IK	39	M	13 DAYS	NORMAL	TV	Candida	PROB	PULM EMB	5 MONTHS
10)LN	23	M	1 DAY	?RHD	MV	NEG	DEF	STROKE	3 MONTHS
11) TT	42	M	10 DAYS	RHD	MV	NEG	PROB		3 MONTHS
	32	M6 F5	7 DAYS				DEF 7 PROB 2 ABSENT 2		

DIED				NATIVE	CULTURE	ECHO	VALVE	CAUSE D	TIME FROM DIAG	COMPLIC
1) WB	36	M	2 WEEKS	NORMAL	S.pneumon	DEF	TV	SEPSIS	22 DAYS	RENAL IMP
2) MM	66	F	2 WEEKS	NORMAL	NEG	DEF	MV	CCF	8 DAYS	
3) AJ	75	M	1 WEEK	NORMAL	S.aureus	DEF	MV	SEPSIS	14 DAYS	RENAL IMP
4) CC	51	M	1 WEEK	NORMAL	NEG	DEF	AV	SUDDEN ?	3 WEEKS	RENAL IMP; INFARCTS+++
5) AH	27	F	1 WEEK	NORMAL	S.aureus	ABSENT	MV	SEPSIS	1 WEEK	LT HEMI, BRAIN ABSCESS
6) JM	66	M	2 MONTHS	NORMAL	S.aureus	PROB	AV	CCF	10 DAYS	
7) NN	50	F	2 MONTHS	RHD	NEG	DEF	AV	CCF	ABSCOND	
8) CR	30	F	1 WEEK	RHD	S.mitior	ABSENT	MV	CCF	6 WEEKS	
9) VS	26	F	2 WEEKS	RHD	NEG	DEF	AV	RENAL FAIL	6 MONTHS	RENAL IMP
10) VK	65	M	5 DAYS	RHD	S.mitior	PROB	AV&MV	CCF	ABSC	TIA'S
11) MP	50	M	2 MONTHS	MVP	Q-FEVER	DEF	MV	RENAL FAIL	6 MONTHS	RENAL IMP
12) SP	24	M	4 DAYS	RHD	NEG	DEF	MV	CCF	ABSCOND	
	47	M7 F5	21 DAYS			DEF 8 PROB 2 ABSENT 2				

DIED POST SURG					CULT	VEG	VALVE	IND SURG	TIME FROM DIAGNOS	COMPL	CAUSE DEATH
1) JM	41	M	6 MONTHS	RHD	NEG	DEF	AV&MV	CCF	6 WEEKS		SURGERY
2) NT	18	F	1 MONTH	RHD	NEG	DEF	MV	CCF	6 WEEKS	SUBAR H	SUBARA HEM
3) MF	67	F	6 WEEKS	DEG AVD	NEG	ABSENT	AV	SEPSIS	1 MONTH	CVA,DIAL	SEPSIS

CHARACTERISTICS OF PATIENTS
WITH RENAL IMPAIRMENT

INITIALS	AGE	SEX	UNDERLY VALVE	CULTURE	VEGETAT	VALVE	CREATININE		DIALYSIS	OTHER COMPLICATIONS
PROVEN IE : SURGERY							ADMIT	DISCH		
1) EP	35	M	NORMAL	NEG	DEF	A&MV	535	53	YES	SEIZURES
2) BK	48	M	RHD	NEG	DEF	AV	150	140	NO	
3) RJ	50	M	RHD	NEG	DEF	AV	320	150	YES	
4) DP	57	M	MVP	NEG	DEF	MV	368		NO	
5) MN	33	M	RHD	NEG	DEF	MV	712	211	NO	
6) MH	27	M	RHD	NEG	DEF	AV	550	259	YES	
7) EB	29	M	NORMAL	NEG	DEF	AV	220	132	NO	ABSENT FOOT PULSE
8) DW	71	M	MVP	?Coryneb	ABSENT	MV	473	211	NO	
9) PH	43	F	RHD	Staph au	ABSENT	MV	167	122	NO	FINGER GANGRENE
DIED										
1) WB	36	M	NORMAL	S.pneumon	DEF	TV	191		NO	
2) AJ	75	M	NORMAL	S.aureus	DEF	MV	168		NO	
3) CC	51	M	NORMAL	NEG	DEF	AV	405		NO	
4) VS	26	F	RHD	NEG	DEF	AV	1241		YES	
5) MP	50	M	MVP	Q-FEVER	DEF	MV	590		NO	
DIED POST SURG										
1) MF	67	F	DEG AVD	NEG	ABSENT	AV	534		YES	

APPENDIX 3

CHARACTERISTICS OF PATIENTS
WITH NEUROLOGICAL COMPLICATIONS

INITIALS	AGE	SEX	SYMP DUR	UNDERLY VALVE	CULTURE	VEGETAT	VALVE INVOLVE	NEURO COMPLIC	INVESTIGATIONS CT SCAN	ANGIO	OTHER COMPLIC
PROVEN IE : SURGERY											
1) CF	47	F	1 MONTH	MVP	Str vir	PROB	MV	VII PALSY	NORMAL	NORMAL	ABS RT DP
2) EP	35	M	6 MONTHS	NORMAL	NEG	DEF	A&MV	STATUS SEIZURES	NORMAL		DIALYSIS
3) JN	48	M	4 DAYS	NORMAL	NEG	DEF	AV	STROKE :	INTRACER HEM	INACC MYC AN	ABS DP
4) DP	69	M	3 MONTHS	NORMAL	S.bovis	DEF	AV	TIA'S			
5) RS	45	M	1 DAY	RHD	NEG	DEF	AV	SEIZURES	INFARCTS	NORMAL	
PROBABLE IE : MEDICAL											
1) LF	17	M	1 DAY	RHD	NEG	DEF	AV	STROKE	INTRACER HEM	MYCOT AN	AN CLIP
2) LV	10	M	3 DAYS	RHD	a-hem Str	DEF	MV&AV	STROKE	NORMAL		
3) LN	23	M	1 DAY	?RHD	NEG	DEF	MV	STROKE	INTRAC HEM		
DIED									POST MORTEM		
1) AH	27	F	1 WEEK	NORMAL	S.aureus	ABSENT	MV	STROKE :	BRAIN ABSCESS		
2) VK	65	M	5 DAYS	RHD	S.mitior	PROB	AV&MV	TIA'S			
DIED POST SURG											
1) NT	18	F	1 MONTH	RHD	NEG	DEF	MV	SUDDEN DEATH	SUBARACHNOID HEM		
2) MF	67	F	6 WEEKS	DEG AVD	NEG	ABSENT	AV	STROKE			DIALYSIS

APPENDIX 4

CHARACTERISTICS OF PATIENTS
WITH ARTERIAL EMBOLIC COMPLICATIONS
EXCLUDING NEUROLOGICAL COMPLICATIONS

INITIALS	AGE	SEX	UNDERLY VALVE	CULTURE	VEGETAT	VALVE	IND/SURG COMPLIC	COMPLIC
PROVEN IE : SURGERY								
1) CF	47	F	?MVP	Str vir	PROB	MV	EMBOLI	VII PALSY; EMBOLUS RT FOOT
2) VN	30	F	RHD	NEG	DEF	MV	CCF	ABSENT RT DP
3) JN	18	F	RHD	NEG	DEF	MV	INFECT	OSLER NODE FOOT
4) HK	56	M	RHD	NEG	DEF	AV	CCF	ABSENT RT
5) JN	48	M	NORMAL	NEG	DEF	AV	CCF	MYCOT AN;ABSENT RT DP
6) NJ	35	F	RHD	NEG	DEF	A&MV	CCF	ABSENT RT DP
7) KS	18	M	RHD	NEG	DEF	MV	CCF	ABSENT LT DP
8) RdP	36	M	RHD	S.mitior	DEF	AV	EMB	EMBOLUS RT LEG
9) EB	29	M	NORMAL	NEG	DEF	AV	CCF	ABSENT RT DP; RENAL IMP
10) PH	43	F	RHD	Staph au	ABSENT	MV	CCF	RENAL IMP; GANGRENE FINGER (EMBOLUS)
PROBABLE IE								
1) AD	32	F	RHD	a-hem Str	ABSENT	MV		BRACH ART OCCLUSION
2) IK	39	M	NORMAL	Candida	PROB	TV		PULM EMB

ECHOCARDIOGRAPHIC AND SURGICAL FINDINGS IN PATIENTS UNDERGOING VALVE REPLACEMENT

NO		ECHOCARDIOGRAPHIC FEATURES	SURGICAL FINDINGS	COMMENT
1)	CF	Probable veg on tip ant MV lt. Small effusion.	Large veg ant lt MV Ruptured chordae.	Echo suspect veg.
2)	SJ	Veg on AV prolapse into LV. Probable vegetation on NCC.	Numerous vegs on AV, predominantly LCC and NCC. Large periannular abcess, eroding into base MV.	IE much more extensive th suggested by Echo. Periannular abscess not detected by Echo.
3)	UN	Two vegs on ant lt MV.	Veg on ant lt MV, on ruptured and intact chords. Post lt had no veg.	IE extended onto chords (of MV).
4)	JN	Vegs medial aspect ant lt. Moderate effusion.	Huge effusion. Vegs on LA wall. Huge vegs on ant. and post lt.	Vegs extend onto LA, involve both lt (echo onl ant lt)
5)	EP	MV thickened, with veg on ant lt AV destroyed by vegs. Suspicious lesion on IV septum.	Numerous vegs destroying AV. Numerous vegs on MV (both lts). Small veg on IV septum.	Echo under-estimated ve post lt MV. Otherwise accurate.
6)	HK	Veg on NCC prolapse into LV. Ao dilated. ?Ao root abscess.	Large vegs all 3 cusps. Root abscess between R and LCC.	Vegs more extensive at surgery. Ro abscess suspected.
7)	JS	No vegs.	Huge vegs on AV. AV totally destroyed.	
8)	JN	Veg attached to IV septum, beneath AV. Possible veg on post aortic wall above AV lt. Small effusion.	Small vegs on AV. Further vegs on aortic wall. Large numerous vegs on ventricular septum.	Vegs much mo extensive an numerous tha detected on Echo. Small vegs not de-tected on Ec

9)	AB	Numerous vegs on AV, extending aortic wall. Abscess cavity between Ao and PA involves LCC. Small pericardial effusion.	Vegs on NCC and RCC.	No abscess cavity as described on Echo.
10)	DM	Probable veg on AV (L-transposition)	AV degenerated, not microscopically infected.	Histology confirmed endocarditis No veg seen surgery.
11)	NJ	Large veg NCC AV, prolapses into LV.	Destroyed AV. Vegs on all cusps. Vegs also present on MV post lt and chordae.	Echo under-estimated AV vegs, and missed MV ve
12)	KS	Extensive vegs on MV. MV thickened, deformed post effusion noted.	Large number vegs on MV.	Echo accurat Extensive ve
13)	LB	Vegs on NCC and LCC of AV. Severe AR, moderate MR.	AV destroyed by IE. Large veg LCC. RCC involved. NCC thickened but no veg.	Echo descrip tion reasona accurate.
14)	DT	Veg on RCC of AV. Possible aortic root abscess. Ao to RV fistula.	AV triable, diffusely damaged. Fistula to RV.	No veg as se on Echo.
15)		Vegs on AV, prolapse into LV.	Extremely large vegs on all three cusps of AV.	Echo accurat
16)	DP	NCC of AV thickened with "healed" veg.	Fibrotic AV.	Veg not detected at Surgery. (6 months later).
17)	RJ	Large veg on RCC of AV. Smaller vegs on other cusps.	Numerous vegs on AV.	Echo accurat
18)	LK	Veg on RCC of AV. AV thickened, AR, MR.	RCC destroyed, large veg. LCC had smaller vegs. NCC retracted.	Smaller vegs LCC missed o echo.

19)	RD	Vegs base of ant lt MV, extending onto AV.	Large vegs Av. No definite vegs on MV. Small aortic root abscess.	Small root abscess (not detected on Echo). Vegs AV (not MV a on Echo.
20)	DP	Veg ant lt MV.	Veg on atrial surface of ant lt.	Echo accurat
21)	MN	Large vegs on MV.	Ruptured chordae with profuse vegs MV.	Echo accurat
22)	SL	Vegs in relation to VSD and on TV and possibly PV. Small effusion.	Numerous small vegs on TV vegs on margins of VSD, and scattered on RV. Large vegs on PV.	Echo missed vegs PV, but otherwise accurate.
23)	BN	Veg out lt MV.	Several vegs ant and post lt.	Post lt vegs not detected on echo.
24)	YA	Vegs on AV. Small effusion.	Thickened AV with veg present.	Echo accurat
25)	TL	Veg on AV.	Small veg AV.	Echo accurat
26)	SG	Dense vegs on AV.	Multiple vegs on AV.	Echo accurat
27)	BM	Vegatrial side of ant lt of MV.	Small vegs on vent surface of AV. Vegs both lt of MV and on the chordae. Vegs lateral wall LA.	Vegs more extensive th described by echo.
28)	AM	Veg on PV. Fistula between AV and RV.	Vegs both cusps PV. Fistula AV to RV.	Echo accurat
29)	MH	Large effusion. Vegs on both AV and MV.	AV destroyed by vegs No veg MV. Ring abscess.	No vegs on M (as seen on Echo). Ring abscess miss by Echo.
30)	MP	Vegs all three cusps of AV. Veg tip of papillary muscle of MV.	Calcified fibrotic AV.	Possibly "headed" veg
31)	EB	Large vegs on AV.	Numerous vegs AV. Root Abscess.	Root abscess missed on Ec
32)	RS	Small veg on NCC of Av.	Small vegs AV.	Echo accurat

33)	DW	No vegs.	No vegs.	Histology confirms end carditis.
34)	CJ	RCC AV has localized echodense thickening - healed veg.	Healed veg NCC Subannular aneurysm.	Echo accurat
35)	MK	Huge veg on AV outflow.	AV destroyed with large veg prolapsing into LV. Old annular abscess. Old vegs on MV.	Echo accurat Old vegs MV.
36)	LD	Huge veg on ant lt MV.	Large veg ant lt MV.	Echo accurat
37)	PH	No vegs detected.	Vegs on MV. Destroyed MV.	Echo missed on MV.
101)	JM	Veg NCC of AV. Small effusion.	Vegs on all lt of AV.	Echo under-estimates extent of ve
102)	NT	MV destroyed. Flail chordae and vegs present.	MV completely destroyed. Multiple vegs both lts and extend onto LA wall.	Echo not fin LA vegs.
103)	MF	No vegs seen.	Fresh vegs of AV Annular abscess.	Abscess and vegs not detected by ehco.

veg - vegetation(s); AV - aortic valve; LV - left ventricle; MV - mit valve; ant - anterior; post - posterior; lt(s) - leaflet(s); IE - endocarditis; Echo - echocardiography; (N)(L)(R)CC - (non)(left)(right coronary cusps; IV - intraventricular; Ao - aorta; PA - pulmonary artery; (P)(T)V - (pulmonary)(tricuspid) valve; LA - left atrium.

HISOTOLOGICAL FEATURES OF EXCISED VALVES IN PATIENTS REQUIRING SURGERY

1)	Numerous Gram positive cocci in veg. Active infective endocarditis.	Gram positiv cocci.
2)	Fibrin veg, occasional clusters of netrophils. No bact. colonies.	Acute endocarditis
3)	Subacute inflammatory process. Fibrosis, vascularization. Superficial vegatation with neutrophilic infiltration. No organisms.	Subacute endocarditis
4)	Fibrotic valve with numerous vegetations.	Subacute endocarditis
5)	Extensive vegetations on aortic and mitral valve. No organisms. Organising acute inflammatory exudate.	Subacute endocarditis
6)	Fibrosis, calcification with vegetations. Gram positive cocci identified.	Gram positiv cocci.
7)	Necrotizing granulomatous infective endocarditis with heavy neutrophilic infiltration. No organisms demonstrated.	Acute endocarditis
8)	Vegetations with varying degrees of organization. No organisms demonstrated.	Subacute endocarditis
9)	Fibrosis, granulation tissue, vegetations. Acute on chronic inflammatory infiltrate. No organisms demonstrated.	Acute endocarditis
10)	Acute endocarditis superimposed on a chronically damaged valve. No organisms seen.	Acute endocarditis
11)	Fibrosis with inflammatory changes. Brish polymorph response. Bacterial colonies on aortic valve.	Bacterial colonies see
12)	Distorted fibrosed vascularized tissue.	Macroscopic extensive vegetations.
13)	MV submitted (not AV)	-----
14)	Fibrosis, calcification of AV.	Histology negative for endocarditis
15)	Numerous gram positive cocci within vegetation.	Gram stain positive.

16)	Calcification, nodular fibrosis, neovascularization. Plasma cell infiltrate.	No evidence for endocarditis.
17)	Vegetations with non-specific inflammatory infiltrate.	Subacute endocarditis
18)	Fibrosis, vascularization. Chronic inflammatory infiltrate. No organisms.	Non-specific inflammation
19)	Ulcerated, granulation tissue. Bacterial colonies demonstrated.	Bacterial colonies.
20)	Connective tissue.	Negative for endocarditis
21)	Fibrosis, revascularization with a vegetation composed of fibrin and inflammatory exudate. No organisms.	Treated subacute endocarditis. Culture positive.
22)	----	-----
23)	----	-----
24)	Organising surface fibrin vegetations. No organisms.	Subacute endocarditis
25)	Non-specific mononuclear cell infiltrate.	Non-specific inflammation
26)	Acute inflammatory infiltrate.	Acute endocarditis.
27)	Fibrinous vegs with acute inflammatory exudate.	Acute endocarditis.
28)	----	-----
29)	Chronic inflammatory exudate - partially treated endocarditis. No organisms.	Subacute endocarditis
30)	Non-specific mononuclear infiltrate.	Non-specific inflammation
31)	Marked active chronic inflammatory infiltrate. Number of vegetations present. No organisms.	Subacute endocarditis
32)	-----	-----

33)	Mild active endocarditis. No vegetation.	Acute endocarditis. Culture positive.
34)	Hyalinized fibrous tissue. No acute inflammation. No organisms.	"Healed vegetation.
35)	Vegetation not submitted - sent for culture.	Peptococcus cultured.
36)	**Vegetations with inflammatory response. Gram positive organisms detected.**	**Gram positiv organisms**
37)	-----	-----
101)	Inflammatory polymorph infiltrate. No organisms.	Acute endocarditis.
102)	**Vegetations with acute inflammatory exudate**	**Acute endocarditis**
103)	Ulcerated vascularized valve with acute on chronic inflamation. No organisms.	Acute endocarditis.