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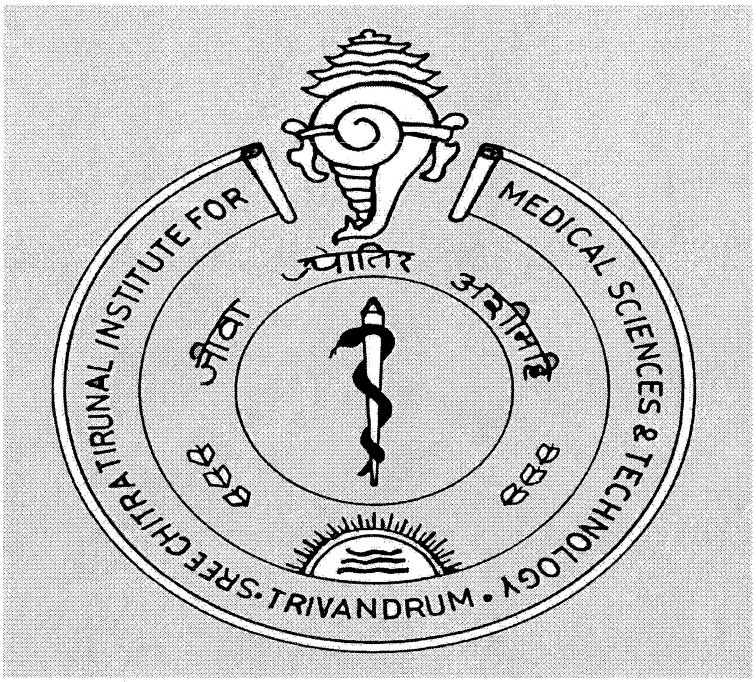

PROJECT REPORT

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MONTH & YEAR OF SUBMISSION : OCTOBER, 2008

CERTIFICATE

I, Dr. Ragesh P, hereby declare that the projects submitted in this volume were undertaken by me under the supervision of the faculty, Department of Cardiology, SCTIMST.

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Date: 7/10/08

CERTIFICATE

This is to certify that the projects entitled "***A STUDY ON CLINICAL PROFILE OF INFECTIVE ENDOCARDITIS***" **and** "***SYSTEMIC VENOUS ANOMALIES-CLINICAL,MORPHOLOGICAL AND ELECTRO CARDIOGRAPHIC CORRELATION"*** are bonafide works of Dr Ragesh P, conducted under the supervision of the faculty in the department of Cardiology ,Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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Trivandrum

Date: 7/10/08

Dedicated to my parents and teachers

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A STUDY ON CLINICAL PROFILE OF INFECTIVE ENDOCARDITIS

PROJECT 2:
SYSTEMIC VENOUS ANOMALIES –CLINICAL,MORPHOLOGICAL AND ELECTRO- CARDIOGRAPHIC CORRELATION.

Project 1

A study on clinical profile of infective endocarditis

Introduction

Infective endocarditis (IE) is an infection of the cardiac endothelium ,macroscopically seen as vegetations. Mortality rate remains as high as 25% for both native and prosthetic valve endocarditis, despite modern medical and surgical therapy. The incidence of Infective endocarditis has remained constant over the past 30 years ,accounting for one case per 1000 hospital admissions. An estimated 10,000-15,000 new cases are diagnosed in United States each year. The incidence has increased in the elderly and in illicit injection drug users. There has also been and increase in acute cases ,prosthetic valve infections and cases due to gram negative, rickettsial ,chlamydial ,fungal and fastidious infections.

The situation in India is quite different .In contrast to the developed countries rheumatic heart disease is still a common predisposing factor .On the other hand MVP and intravenous drug abuse endocarditis which are common causes of endocarditis in the West are rare in India .Besides this, the mortality of Infective endocarditis in India is high due to the less aggressive surgical strategy offered to patients .

There are few studies in Infective endocarditis from India , but majority are from the North . There are no major studies on IE from South India. There is a high frequency of IE admissions and prosthetic valve endocarditis in this part of the country .The prognosis of IE, the predisposing factors ,microbiology and predictors for mortality are not known in this population. Though early aggressive surgical strategy is not followed here ,the impact of surgical treatment in reduction of mortality has not been studied ;especially in the background of contradictory reports on the effect of early surgery from the West .

This study was undertaken with these specific objectives in mind.

Review of Literature

History

Sir Jean Francois Fernel of France is credited with the earliest description of endocarditis in the book Medicini in 1554. Later in 1646 an Italian physician Lazarus Riverius, gave a graphic description of Infective Endocarditis (IE). He gave a description of the post mortem findings in a man who died from cardiac failure - "In the left ventricle ...round carbuncles were found ...which resembled a cluster of hazelnuts and filled up the opening of the aorta". Although other descriptions followed, Boulliard in 1841 was the first to recognize this condition as a form of endocarditis and to distinguish it from rheumatic carditis. Shortly after this, Virchow in 1847 observed that the vegetations were not as was generally stated, simple depositions of fibrin. In the autopsy study, he described vegetations on the posterior mitral valve cusp as "on this a ragged fringed hanging fibrous coagulum 4 inches long in some places degenerated into a reddish pus like pulp". The next major advance was made by a Norwegian pathologist E.F.H .Winge in 1869. He gave the first indication that Infective Endocarditis was of bacterial origin when he saw under the microscope "short rod shaped or round bodies" in what he described as a parasitic vegetation. In 1885, Sir William Osler lectured on this subject of malignant endocarditis - "It is of use from time to time to take stock ,so to speak , of our knowledge of a particular disease , to see exactly where we stand in regard to it , to inquire to what conclusions the accumulated facts seem to point ,and to ascertain in what direction we may look for fruitful investigations in the future". With these words, William Osler began the first of three seminal lectures on endocarditis to the Royal College of Physicians of London in 1885. As modern medicine moves into the 21st century after decades of rapid scientific advancement it is once again appropriate to "take stock". This and his subsequent writings provide a marvelous overview of the

pathogenesis and clinical features of endocarditis. Most of his observations are valid even today.

Epidemiological studies in the opening decade of this century showed clearly the toil which Infective Endocarditis took on the lives of patients with rheumatic and congenital heart disease. It was responsible for upto one third of all deaths in these groups. A fatal outcome was virtually inevitable and resulted from sepsis, emboli and cardiac failure with anemia an important contributing factor. Dr Paul White,s an American cardiologist found that of 250 well documented cases only one survived although other workers reported cures by ligation of an infected PDA, and a few others were attributed to the use of antimeningococcal and antipneumococcal sera. The therapeutic use of sulfonamides was very disappointing but the introduction of penicillin in the early 1940's was dramatically effective. Cure rates of 75-85% were claimed better than in some recent reports. This is at least partly because they took no account of relapses, recurrences and subsequent deaths from cardiac failure. Nevertheless it was the turning point into the treatment of Infective Endocarditis and in terms of lives saved and prolonged, it outweighs any subsequent innovation.

More than 100 years after Osler's lectures this serious infection can still remain a diagnostic and therapeutic dilemma. It's name has been changed several times, first to "bacterial endocarditis" and subsequently to "Infective Endocarditis" after the observation that microbiologic agents other than bacteria may cause the disease. In the early years of the new millennium, Infective Endocarditis still proves to be difficult to diagnose and is associated with a high death rate 21–35% .The lack of impact of modern medicine reflects important changes in the causes of the disease. In Western populations in particular, chronic rheumatic heart disease is now an uncommon antecedent, whereas degenerative valve disease in elderly people, intravenous drug misuse, preceding valve replacement or vascular instrumentation have become increasingly frequent, coinciding with an increase in staphylococcal infections and those due to fastidious organisms. Furthermore, previously undetected pathogens are now being identified with the disease, and multi drug resistant bacteria challenge conventional treatment regimens.

infections are attributed to congenital abnormalities in children more than two years of age .In the very young, pediatric IE more commonly occurs in the setting of normal cardiac structures and is usually related to catheter related blood stream infections .[12] Infective endocarditis occurs at least twice as often in men than women.[13] This ratio increases to 9:1 in patients 50-60 years of age and and to 6.5:1 in individuals 61-70 years of age . This sexual distribution generally is not dependent of the specific infecting organism . However, women less than 35 years of age are disproportionately involved in cases of enterococcal endocarditis.[14]

Predisposing cardiac lesions

Approximately 40% of cases of IE affect the mitral valve alone and 5-36% affect the aortic valve alone .Infections of both these valves occurs less often.[15] The pulmonic valve is seldom affected. Cases of right sided endocarditis occur primarily in intravenous drug abuse and health care associated infective endocarditis.

Almost any structural cardiac lesion of the heart may give rise to IE as long as it can result in formation of a sterile platelet/fibrin thrombus ,the indispensable precursor of all types of IE. The specific type of cardiac abnormality underlying a given case of IE is closely associated with certain characteristics of the patient(age, history of drug abuse ,or immunosuppression) and the nature of the infecting organism .Bacteria ,such as streptococcus viridans ,with a low invasive potential ,opportunistically infects abnormal heart valves. Staph aureus has the ability to infect normal valvular structures. Cabell and Autyn commented that " there are studies available to quantify the risk of developing IE for patients with specific cardiac conditions .It is more clear which conditions when associated with active IE are more likely to be associated with complications and death".[16] For certain conditions ,the risk of developing IE is better established .In the case of mitral valve prolapse (MVP) with significant regurgitation,it is increased to 10-100 fold[17],whereas for prosthetic valves and for patients with prior IE, the risk for valvular infection may be increased more than 100 fold .[18, 19]

Durack and Petersdorf [20] have concluded that the advent of antibiotics has made no change in the contribution of congenital heart disease to the development of IE.

Overall ,congenital heart disease is the underlying factor in 5% of adult IE. Bicuspid valves may account for up to 20% of the cases of IE in individuals older than 60 years. Among congenital heart diseases ,the tetrology of Fallot exhibits the greatest incidence of IE. Even when surgically corrected, it remains a significant factor for the development of endocardial infection .Approximately 25% of tetrology patients who undergo and anastomotic correction, develop infection at the surgical site. This is attributed to turbulent flow at the site where vessels are joined . Secundum atrial septal defect and pulmonary stenosis pose negligible risks for IE ,probably because of the minimal pressure gradient across these lesions.[21,22] The risks of congenital aortic stenosis becoming infected is directly proportional to the pressure gradient across the valve.[23].

Although RHD has become a negligible predisposing factor for IE[7,24] in the developed world ,it remains the largest cardiac risk factor for IE in the developing countries accounting for 50% of cases . The lifetime risk for patients with RHD to develop endocardial infection is 6%.[7] The majority of cases of IE complicating RHD occur in females (67%) of cases, and involves the mitral valve (85%) .

Mitral valve prolapse accounts for up to 30% of cases of native valve endocarditis in the developed countries. It has supplanted RHD as the chief underlying condition for the IE of younger patients.[17,25,26] Mitral valve prolapse is found in approximately 5% of the population . Cases of MVP that do not exhibit any significant regurgitation are at little increased risk of development of IE.[27]

In degenerative valve disease and asymmetric septal hypertrophy ,the risk of developing IE is directly related to the level of obstruction – the higher the peak pressure ,the greater is the chance of infection.[28,29]The lifetime risk of developing IE in these patients is is 5%. Streptococcus viridans is the causative organism in 75% of cases .

Infective endocarditis occurs in approximately 5-10% of prosthetic valves.[30] The greatest risk of infection occurs within two months of implantation (early PVE).Initially mechanical prosthetic valves are more vulnerable. With time, the rate of infection of bioprosthetic valves equals or exceeds that of mechanical ones .After the first year, the rate of infection averages about 0.3%. Over time, the process of

endothelialization partially protects prosthetic valves from being infected by transient bacteremias. However it is important to emphasize that no matter how old the valve is ,it will always be at some risk . [31] Prosthetic valve endocarditis accounts for 7% of the total cases of IE.[32,33] Similar in nature to PVE is IE of pacemakers and other intracardiac devices.[34] Most become infected within a few months of implantation.

Pathology of infective endocarditis

The sine qua non of IE is the vegetation. These are friable fibrinous excrescences that develop along the endocardial surface. Most vegetations of IE are polypoid,but they can alternatively be sessile. Vegetation vary in size ,in part dependent on the causative organism ,the length of infection, and whether they affect the left or right heart. In Q-fever, vegetations may be inconspicuous ,exhibiting only a thin coating of fibrin along the valve surface.Bulky vegetations occur on the tricuspid valve reflecting the virulence of the organisms that affect the tricuspid valve and the lower systolic pressures of the right ventricle .They are white or yellow as opposed to the dark red vegetation on the left sided valves.

This first valid explanation of the sites of endocardial infection was advanced by Lepesckin in 1952. He believed that mechanical and hydraulic forces played an important role in the development of IE. He based his conclusion on his study of 1024 autopsied cases of IE.[35] This documented that 86% of cases involved the mitral valve;55% ,the aortic valve;19.6% the tricuspid valve and 1.1% the pulmonary valve. These findings suggested that the rate of valvular involvement was directly related to the hydraulic and mechanical stress to which it was exposed .In 1963, Rod Bard documented that the contribution of the Venturi effect to both the pathogenesis of the location of non bacterial thrombotic endocarditis.[36]He injected an aerosol of bacteria into a stream of air passing through an agar Venturi tube from a higher pressure source into a lower pressure sink replicating the characteristic pattern of IE with the maximum concentration of bacteria appearing in the lower pressure area immediately beyond an intracardiac constriction owing to decreased lateral pressure on the walls of the tube.[38]

Complications of infective endocarditis

Cardiac complications

Congestive heart failure is a major complication of infective endocarditis. There are multiple pathways that lead to heart failure in IE including 1)valvar insufficiency 2)valvular stenosis 3) rupture of infected fistulous tract and 4) conduction system abnormalities.

Valvular insufficiency is the most common complication of IE.It reflects either destruction of the valve by tears or penetrations ,or loss of structural support by tethering chordae or the valve ring . In mechanical prosthetic valves, direct involvement of silastic balls or metal discs and rings is unusual but paravalvular leaks secondary to dehiscence of the sewing ring are common.Vegetations may interfere with the mechanics of the valve during the cardiac cycle leading to both stenosis and regurgitation.

Abscesses of the mitral valve can form fistulous tracts between the left ventricle and the right side of the heart .Abscesses of the aortic sinuses of valsalva can lead to fistulous tract that communicate with the right atrium or right ventricle leading to acute right heart failure owing to massive left to right shunting. Periaortic valvular abscesses can extend directly into the adjacent atrioventricular node causing conduction of AV node block and fascicular block.

Graupner et al[37]in a prospective study of 211 patients with left-sided endocarditis detected perivalvular complications in 37% . The incidence of periannular extension of infection in native and prosthetic valves was 29% and 55%, respectively. The presence of prosthesis (relative risk [RR] 1.88) and previous endocarditis (RR 1.78) were the only pre-existing heart conditions associated with perivalvular complications. Aortic infection (RR 1.8) and the development of atrioventricular (AV) block (RR 2.55) were related with the existence of these complications. Coagulase-negative staphylococci were very common in patients with perivalvular complications (RR 1.77) and small vegetations

were more frequent in these patients (RR 1.45). An operation was more frequently performed in patients with perivalvular complications but mortality was similar in patients with and without these complications.

Manzanoa et al [38] reports ACS as an uncommon complication in patients with endocarditis with a frequency of 2.6%. It normally occurs in the acute phase of the disease (first 15 days) and is more often associated with virulent microorganisms like Staph aureus, aortic valve infection (12 out of 14 cases), severe valve regurgitation, and large periannular complications. The mechanism responsible for myocardial ischemia was coronary embolism in 3 out of 11 of their patients and extrinsic coronary compression by these periannular complications in the rest. ACS complicating IE is associated with high incidence of CHF,heart block and mortality in patients with endocarditis.

Embolic complications

Embolic complications are common in infective endocarditis .Involvement of tricuspid valve with virulent organisms like Staph aureus or Candida species is associated with bulky vegetations that fragment and travel to the lungs . As vegetations are composed of both infected and bland fibrin –platelet excrescences, the result is a potential mixture of bland pulmonary infarctions and septic pulmonary abscess. Micro thrombi can travel through patent foramen ovale to produce embolic complications on the left side of the circulation. Emboli on the left side of circulation may affect virtually any organ, but cerebral emboli are of greatest clinical concern. Approximately 20% of the patients with IE develop cerebral emboli with an associated mortality of approximately 40%.[39] Hemorrhages and cotton-wool Roth spots reflect septic emboli to the microcirculation of the retina. Splenic emboli can cause flank pain or diaphragmatic irritation, but may also be symptomatically silent . Renal microemboli produce a classic flea bitten appearance of the cortex with focal segmental necrosis of the glomerular tuft. Janeway lesions are caused by microemboli to the skin whereas Osler's nodes are caused by arteriolar injury owing to immune complex deposition.

Schunemann et al[40] analyzed the risk factors for embolism in 177 consecutive patients with IE. Major embolic complications occurred in 40% of all patients. In NVE, a

higher rate of embolic events (45% vs. 26%; $p < 0.05$), and a larger vegetation size compared to PVE was observed (14 +/- 6 mm vs. 11 +/- 5 mm; $p < 0.05$). The most important risk factor for embolic complications in NVE was Staphylococcus aureus (odds ratio 6.4). Furthermore, double valve endocarditis, fever, and mitral valve endocarditis were associated with the risk for embolism. In PVE, fever was a risk factor for embolic events. Staphylococcus aureus was also a frequent microorganism in embolism (45% vs. 22%). The in-hospital mortality was significantly increased in case of embolism (NVE 40% vs. 11%; $p < 0.001$; PVE 36% vs. 9% $p < 0.05$). About 50% of all embolic events occurred before admission. In patients with NVE, aspirin therapy because of coronary artery disease appeared to reduce the rate of embolic complications (11% vs. 47%) however, there were only a few patients on aspirin (9%) in his study .

Neurological complications of IE

Heiro M et al [41] identified neurologic complications in 25% of the infective endocarditis patients with an embolic event as the most frequent manifestation(42%). In the majority (76%) of episodes, the neurologic manifestation was evident before antimicrobial treatment was started, being the first sign of IE in 47% of episodes. Only 1 recurrent cerebral embolization was observed. Neurological complications were significantly associated with Staphylococcus aureus infection (29% vs 10%; P =.001) and with IE affecting both the aortic and the mitral valves (56% vs 23%; P<.01), Death during the acute phase of IE occurred in 24% with neurological complications and in 10% without neurological complications (P<.03).These results reinforce the belief that rapid diagnosis and initiation of antimicrobial therapy may still be the most effective means to prevent neurological complications

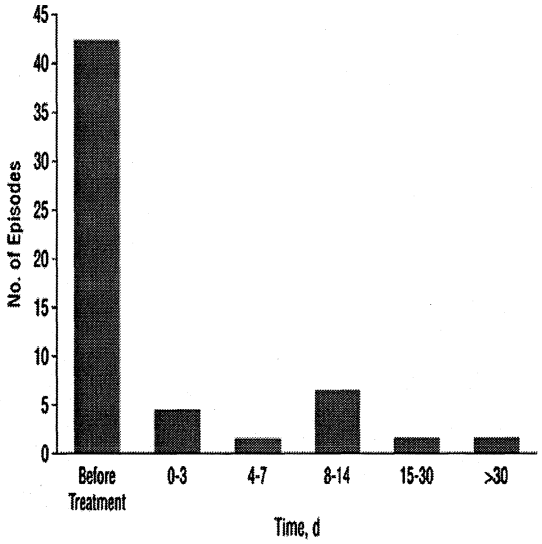

Figure 1. The occurrence of neurologic manifestations during 55 episodes of infective endocarditis. The number of episodes is presented in relation to the initiation of antimicrobial treatment (in days) .(From Heiro M [43])

Snygg-Martin et al [42] analyzed the neurologic manifestations of IE by sensitive methods in 60 patients .They performed neurological examinations and magnetic resonance imaging of the brain, and cerebrospinal fluid analyses of inflammatory and neurochemical markers of brain damage (neurofilament protein and glial fibrillary acidic protein) in all patients with left sided IE. They observed cerebrovascular complications (CVC) in 65% (35% symptomatic and 30% silent) .In their study also, majority of complications occurred early before antibiotic treatment .They found no fresh neurological deterioration after surgery in patients who were established to have symptomatic CVC preoperatively. A larger heart valvular vegetation size was a risk factor for both symptomatic and silent CVCs. Staphylococcus aureus etiology conferred a higher risk only for symptomatic cerebral complications .

Prosthetic valve endocarditis (PVE)

PVE that is clinically evident within 60 days of valvular surgery is termed early PVE. Those cases that are evident past 12 months are considered as late PVE.

Intermediate PVE occurs between 2 and 12 months after implantation.[43] PVE is 5 times more frequent in patients whose prosthetic valve is implanted during active infection.[44] This situation where the prosthesis was placed because of an infected valve is called secondary PVE.When PVE develops in a valve that replaced a non infected one ,it is termed primary PVE. [45].Common denominator behind all types of IE is the sterile platelet/fibrin thrombus or non bacterial thrombotic endocarditis .[46]After prosthetic valve is implanted ,it undergoes a process called conditioning .The first stage is a non specific reaction that varies with particular shape of implanted material as well as physico chemical composition of the prosthesis .Various body fluids ,especially blood (fibronectin and fibrinogen) and tissue proteins as well as cells bind to the prosthetic material .These protein components may either promote or interfere with staphylococcal attachment to the valve.[47,48] In general ,they promote the adherence of staphylococcus aureus but interfere with that of coagulase negative staph aureus (CONS). The second phase of conditioning is the deposition of fibrin/platelet thrombi (Non bacterial thrombotic endocarditis-NBTE) at the interface of the native cardiac tissue and the sewing cuff that has not been endothelialized.[49] Until it is endothelialized at approximately 60 days after placement , the sewing cuff remains susceptible to the deposition of platelets and fibrin . At about 60 days ,the annulus and sewing cuff becomes encased in endothelial cells . However, these layering cells do not function normally in preventing localised thrombus formation because of this ,the cuff remains susceptible to infection throughout the life of the valve.Albeit at a low frequency than earlier. The anchoring sutures ,themselves, serve as a conduit for organisms to invade the adjacent cardiac tissues .This process may result in formation of paravalvular leaks and ring abscesses.[50,51] The sewing cuffs of bioprosthetic valves are equally prone in becoming infected . In addition, their leaflets are vulnerable to infection in a manner quite similar to that of the native valves.[52,53] Over a period of many years, the blood flow through the valve damages the surface of the leaflets of bioprosthetic valves. This roughening of the surfaces leads to the deposition of micro thrombi (NBTE) to which circulating bacteria may eventually adhere ,as well as calcification of the leaflets. From the infected thrombi, bacteria may invade the cusps of the valves despite their being pretreated

with glutraldehyde .This chemical partially protects the porcine valvular leaflets and bovine pericardial tissue from infection.[54,55] Enlarging thrombus , by further disturbing the smooth rheology of blood flow ,contributes to the growth of either an infected thrombus or NBTE.

In almost all cases of early PVE and many intermediate PVE, the bacteria are nosocomial are health care- facility related.Seventy five percent of the cardiopulmonary bypass equipments were found to be contaminated by organisms that cause early PVE (coagulase negative staph,streptococci,gram negative aerobes,diphtheroids and fungi). The ambient air is the major source of bacterial contamination . The concentration of organisms in the air of the operating suit appears to be directly related to the amount of personnel present .Seventy one percent of cultures of the valve and its bed ,obtained just before the closure of the sternal wound have been positive .Most early PVE,has been because of infection secondary to intravenous lines ,including pacer wires and wound infections.[56,57] Water which is documented by species of legionella (L.Pneumophilia and L.Dumoffi) has been documented by means of restrictive DNA analysis as a source of early legionella PVE.[58]

Romano G et al[59] compared preoperative and intraoperative features, and long-term outcome of 353 patients operated on for native (NVE) and primary prosthetic valve endocarditis (PVE). The PVE patients were older, presented with more compromised clinical conditions, and had worse early and long-term outcomes than NVE patients. PVE had a higher incidence of recurrence and worse prognosis, especially if the mitral valve was involved.

Larbalestier et al [60]analyzed 158 patients who underwent surgery for IE out of which 109 had native valve endocarditis (NVE), and 49 had prosthetic valve endocarditis (PVE). The male to female ratio was 2:1 with a mean age of 49 years . Sixty four percent were New York Heart Association functional class IV before surgery, and 12% of the group had a history of intravenous drug abuse. In both NVE and PVE groups, Streptococcus was the predominant infecting agent. Uncontrolled sepsis, progressive congestive failure, peripheral emboli, and echocardiographically demonstrated vegetations

were the most common indications for surgery. The operative mortality was 6% in NVE and 22% in PVE. Long-term survival at 10 years was 66% for NVE and 29% for PVE. Freedom from recurrent endocarditis at 10 years was 85% for NVE and 82% for PVE. The main factors associated with decreased survival overall were PVE and nonstreptococcal infection.

Guodong Fang et al [61] evaluated patients with bacteremia at 1, 2, 6, and 12 months after its occurrence. Of 171 patients,43% developed endocarditis: Fifty-six (33%) had prosthetic valve endocarditis at the time bacteremia was discovered ("endocarditis at outset"), whereas 18 (11%) developed endocarditis a mean of 45 days after bacteremia was discovered ("new endocarditis"). Mitral valve location and staphylococcal bacteremia (Staphylococcus aureus or S. epidermidis) were significantly associated with the development of "new" endocarditis. Twenty-one patients without evidence of endocarditis at the time of bacteremia received short-term antibiotic therapy (<14 days)out of which,1 patient (5%) developed endocarditis. Eleven of 70 patients (16%) who received long-term antibiotic therapy (>14 days) also developed endocarditis ($P > 0.2$).

They conclude that bacteremic patients with prosthetic heart valves were at notable risk for developing endocarditis, even when they received antibiotic therapy before endocarditis developed and regardless of the duration of such therapy. Intravascular devices were a common portal of entry for bacteria .

Mortality in Infective endocarditis

Mansur, in 1992 reviewed 300 episodes of IE in 227 patients, which occurred between 1978 and 1986.[62] Two thirds of these cases had significant complications when on antibiotic therapy. This was true for individuals with native or prosthetic valve infections. These investigators postulated that undesirable outcomes in IE were related to complications. They defined these as embolic, cardiac and immunological. Their appearance was not necessarily associated with microbiological course of the valvular infection .Cardiac failure developed in 1/3 rd of the patients. This is consistent with other studies that estimate that congestive heart failure is present in 15-65% of the patients.[63]This report documents that congestive heart failure is less often a cause of death

than it was in the past. Formally cardiac decompensation was the leading cause of death.[64]This diminution is most likely the result of the current aggressiveness of the diagnosis and surgical correction of valvular decompensation at a relatively early stage. The central nervous system was the second most frequent site of infection with mycotic aneurysm and cerebral abscesses. The valve IE and prosthetic valve IE had identical rates cerebral embolism and intracerebral mycotic aneurysms. Twenty one percent of patients had sepsis syndrome with staph aureus being the most commonly associated organism. Drug reactions occurred in 14% of the patients. Although cardiac complications were reported more frequently ,death occurred most often in those with cerebral involvement or sepsis. Mortality rate in IE of intracranial mycotic aneurysm approaches 60%; if detected prior to rupture ,this figure is 30% .After their rupture, mortality is at least 80% . Mycotic aneurysm of the cerebral vessels develop in 2-10% of patients with IE.[65,66] Cerebral angiography is the diagnostic modality of choice. MRI appears promising in its role as a screening test in every patient with IE.In a recent retrospective study of patients with left sided native valve endocarditis,the overall rate of death was 25%.[67] The investigators identified five independent mortality risk factors to which they gave a weighted score. Prediction of 6 month mortality can be calculated from the total score of the risk factors.

The mortality rate of PVE prior to 1980, was 70% and 45% for early and late types respectively .With the recognition that aggressive surgery is necessary in most cases of PVE,mortality was decreased to between 15% and 25% with no relationship between whether the infection is of early or late onset.[68]

Predictors of mortality

Chu et al[69] evaluated 267 consecutive patients with definite or possible IE by modified Duke criteria and echocardiography performed within 7 days of presentation . Acute physiology was assessed by the Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score at the time of presentation, and early heart failure was diagnosed by Framingham criteria. In-hospital mortality rate in the cohort was 19% and similar for patients with definite or possible IE (20% versus 16%, respectively; p=0.464).

Independent predictors of death determined by logistic regression modeling were diabetes mellitus (OR 2.48), Staphylococcus aureus as causative organism (OR, 2.06), APACHE II score (OR, 1.07), and embolic event (OR, 2.79). Early echocardiographic findings of the Duke criteria were not predictive of death.

Surgery in Infective endocarditis

In 1960,Starr and Edwards [70] and Harkness[71] performed the first successful implantation of prosthetic mitral and aortic valves. Wallace et al[72] performed the first valve replacement to treat refractory IE, which lead to cure of the disease. In his review of infectious aspects of prosthetic valves, Weinstein[73]concludes that the cardiac surgeon wields a double edged scalpel that both cures valvular infection and is responsible for inducing it.

Congestive heart failure is the most frequent cause for surgery in IE.Prior to the availability of cardiac surgical techniques,91% of IE associated fatalities were due to CHF.[74] Medical therapy ,alone results in a death rate of 75% in patients with moderate to advanced CHF. Appropriate surgical intervention can reduce this to 25%. [75,76] Heart failure accounts for up to 75% of surgical procedures in IE .[77] Mills et al[78] were among the first to recognize the significant role surgery could play in treating in treating the CHF of IE. In their uncontrolled series ,only one out of 15 patients who were treated medically were alive at 6 months. Nine out of 14 who received combined medical and surgical therapies were still alive. These findings were confirmed by Croft.[79] Survival of the patients who received medical and surgical therapies were clearly superior (56% vs. 11% of those who were treated medically .A meta-analysis of nine retrospective studies published in 1997 ,involving 300 patients in significant heart failure ,demonstrated a 60% versus 29% advantage in survival rate with dual therapy.[80]A major criticism of these studies is that they did not take into account co morbidities such as kidney failure and cerebrovascular diseases that prevented a surgical approach. Although this bias favours the surgically treated group ,the striking difference between the two approaches is likely to remain significant .The difference in survival from PVE associated CHF ,in those treated medically and those

treated surgically and medically ,parallels that of NVE. At 6 months the mortality in the former group approaches 100% .In the surgical cohort 45-85% are alive at this point.[68]For staph aureus PVE[81], a multivariate analysis of the effectiveness of a combined medical and surgical approach compared with a medical approach has been conducted .Even with adjustment of the patient co-morbidities, surgery resulted in a 20 fold decrease in patient deaths.

The individuals who benefited most from surgery are those present with the new onset of significant congestive failure and are operated upon within 4 days on the beginning of treatment.[82,83]The decision to operate is based on hemodynamic factors and not the course of valvular infection. In patients not in failure, the length of preoperative antibiotic therapy has no bearing on intra operative death.[82] The operative mortality of urgent surgery in patients without clinical CHF ranges from 6-11%. This rate increases to 17% to 33% in those with failure.[84]Over time the, valvular insufficiency rises to ventricular dilatation and further insufficiency .This spiral of deterioration converts mild CHF to severe failure usually within the first month of antibiotic therapy.

Severe aortic regurgitation results in a more severe and more rapidly progressive CHF than does mitral valve incompetence. Clinical signs of significant heart failure ,in the presence of heart failure aortic regurgitation ,demand an immediate cardiac surgery consultation.[85]Acute AR with evidence of early closure of anterior mitral leaflet represents an uncomplicated overload of the left ventricle that calls for urgent surgery.[86]Progressive heart failure ,in conjunction with acute aortic or mitral valve incompetence ,likewise demands early surgery.

Mullany et al [87] retrospectively reviewed the microbiologic, clinical, operative findings and the survival data in 151 patients with culture-positive active endocarditis encountered between 1961 and 1991.The mean age was 49.8 years. Native valve endocarditis was present in 86 patients, and prosthetic valve endocarditis (PVE) was diagnosed in 65. The aortic valve was involved in 62% of patients, the mitral valve in 25%, and both valves in 10%. The operative mortality was 26%. The most important univariate determinants of mortality were an abscess at operation (P = 0.01) and renal failure (P =

0.03). A trend toward a higher mortality with PVE and staphylococcal infection was noted. For hospital survivors, the 5- and 10-year survival was 71% and 60%, respectively. Univariate determinants of an adverse long-term survival were annular abscess (P = 0.01), renal impairment (P = 0.01), heart failure (P = 0.02), and aortic valve involvement (P = 0.05). On multivariate analysis, the most important adverse determinants of long-term survival were heart failure (P = 0.02), renal impairment (P = 0.02), and PVE (P = 0.03). Thirty patients required a subsequent reoperation; of these, seven required a second and two a third operation. The most common reason for reoperation was periprosthetic regurgitation without infection (N = 19). Four operations were performed for recurrent endocarditis. At 5 and 10 years, the risk of reoperation was 23% and 36%, respectively. They concluded that though the surgical treatment of culture-positive active endocarditis is still associated with substantial mortality, the long-term outcome of hospital survivors is excellent. Subsequent reoperations for periprosthetic leak are common, but recurrent infection is uncommon.

On the contrary , there is data to suggest that surgery may be less optimal during the active phase of native valve IE unless there is a need for immediate surgery .Aranki et al[88] analyzed the interaction between the various subsets of aortic valve endocarditis (native, prosthetic, healed, and active), timing of surgery, and their influence on early and late outcomes in 200 patients. The mean age was 53 years. Fifty five percent were in NYHA class IV status before surgery. Native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE) were present in 66% and 34% patients, respectively. Surgery was required in 60% during the active phase and 40% during the healed phase of endocarditis. The main indication for surgery in the healed group was progressive congestive heart failure. The major indication for surgery in the active group were congestive heart failure (68%) and continuing active sepsis (70%). They found that the mortality and recurrence was higher after surgery for active endocarditis in native valve .Their data suggests that for active endocarditis, surgery should be delayed to achieve a healed status provided there is no pressing need for immediate surgery. Patients with

staphylococcal endocarditis, particularly on a prosthesis, should be operated on sooner and should be covered with antibiotics

The first randomized study ENDOVAL 1 (216 patients) to compare the efficacy of early surgery (within 48 hours of randomization) versus medical management in IE is underway . Patients with infective endocarditis without indication for surgery will be included if they meet at least one of the following: (1) early-onset prosthetic endocarditis; (2) Staphylococcus aureus endocarditis; (3) periannular complications; (4) new-onset conduction abnormalities; (5) new-onset severe valvular dysfunction. A total of 216 patients will be randomized to either of the 2 strategies. Stratification will be done within 3 days of admission. The end point is 30 day mortality.[89]

Persistent infection/persistent bacteremia

Failure to clear the blood stream infection of IE after 7 days of appropriate antimicrobial therapy is associated with a poorer than average clinical outcome.[90] When metastatic infection has been ruled out, persistent fever usually represents an intracardiac complication (56%).[91] Persistent fever which usually presents 3-4 weeks into apparently successful therapy, is usually because of hypersensitivity reactions to antibiotics, especially the beta lactams.[92] When fever is persistent and or associated with bacteremia ,surgery can significantly reduce the fatality rate from 34-90% to 9-13%. [93]

Persistent infection is almost invariable with fungal IE.Valve replacement should be undertaken as soon as possible in these cases, However the case fatality rate remains high for candidal IE (42%) despite dual therapy. Eighty seven percent of Aspergillus IE succumb[94] ;these dismal outcomes are most likely because of high rates of embolization,metastatic infections (70% of cases overall) perivalvular and myocardial abscesses.[95]Early surgical intervention may improve long –term outcomes.

Vegetations

Vegetations are detectable in up to 78% of cases of IE.[96] The incidence of clinically apparent arterial emboli in IE is approximately 43%. About 27-65 of the emboli involve the cerebral circulation.[97,98,99,100] Twenty five percent of deaths from IE are because of emboli.Seventy five percent of clinically apparent emboli occur before the onset of

antibiotic therapy.[101]It is likely that the incidence of emboli of all types is significantly greater than that reported.

A recent meta analysis indicates that systemic embolization was increased in the presence of vegetations >10mm compared with those of valvular thrombi of 10mm.(37% vs 19%).[102]More definitive studies support the association correlation between embolization and 1) vegetations>10mm,2)those located on the anterior leaflet of the mitral valve,and 3)those with increased mobility.[100,102,103]It is important to emphasize that there is no proof that operating on patients with these characteristics actually pre-empts embolization.[79]

Infective Endocarditis in India

The estimated incidence of IE in the Western population has remained unchanged over the past two decades at 1.7 - 6.2 cases per 100,000 patient years [104,105] but such estimates are not available from India. Even assuming the lowest incidence, at least 17,000 episodes of IE must be occurring per year in India. From the published series[104,106,107,108]it is apparent, as may be expected, that IE in India occurs in relatively young patients with underlying rheumatic and congenital heart diseases.[104] The blood culture is negative in high proportion of cases, the diagnosis is often delayed, and the mortality is substantial. How far the oft-quoted changes in the face of endocarditis (i.e. changes in the causative organisms, patient profile and outcomes) have occurred in India is not clearly known

In comparison with the western series ,Indian series have a higher incidence of RHD (Table 1)and lower incidence of MVP.Reported endocarditis in IV drug abusers in Indian series is rare.Culture positivity is less compared to Western series. Surgery for IE was performed less often in Indian studies compared to the West

Table 1 A comparison of Indian and Western series of infective endocarditis

Characteristics	Indian Series		Western Series	
	Choudhury et al. [108]	**Garg et al.** [109]	**Metanalysis**[109]	**EHS**[110]
Duration	1981-91	1992-2001	1993-2003	Apr – July 2001
Episodes	190	198	3784	159
Age(yrs)	25+/-12	27.6+/-12.7	36-69	56+/-17
Identifiable preceeding portal of entry(%)	15	16.6	NA	41-48
Predisposing condition				
RHD (%)	42	46.9	NA	NA
CHD(%)	33	28.6	NA	NA
PVE(%)	1	10.4	7-25	26
IV drug abuse (%)	0.5	0	15	NA
Echo positive (%)	64	89.9	NA	82
Surgery for IE(%)	1	23	25-40	52
In-hospital mortality(%)	25	21	16	12.6

EHS: European heart survey; RHD: rheumatic heart disease; CHD: congenital heart disease; PVE: prosthetic valve endocarditis; IV: intravenous

. Choudhury R et al [108] analzyzed the clinical data from 186 patients (133 males and 53 females) with 190 episodes of infective endocarditis (IE) occurring between January 1981 and July 1991 from PGI,Chandigarh and compared the data with the West. The mean age was much lower (25 +/- SD 12 years. Rheumatic heart disease was the most frequent underlying heart lesion accounting for 42%. This was followed by congenital heart disease in 33% and normal valve endocarditis in 9%. Twenty-four patients had either aortic regurgitation (n = 15) or mitral regurgitation (n = 9) of uncertain etiology. Prosthetic valve infection and mitral valve prolapse were present in only 2 patients each. A definite predisposing factor could be identified in only 15% patients. Postabortal sepsis and sepsis related to childbirth accounted for 6 and 5 cases, respectively. Only 1 patient had history of intravenous drug abuse. Two-dimensional echocardiography showed vegetations in 64%. Blood cultures were positive in only 47%. Commonest infecting organisms were staphylococci (37 cases) and streptococci (34 cases). Except for a significantly higher

number of patients with neurologic complications in the culture-negative group, there were no differences between patients with culture-positive and culture-negative IE. A significantly greater number of culture-negative patients had received antibiotics than did culture-positive patients (87 vs 23, $p < 0.001$).

Garg et al[109]sudied a total 198 episodes of Duke "definite" infective endocarditis (IE) in 192 patients observed over 10 years in SGPGI,Lucknow . [141 males and 51 females, mean age 27.6+/-12.7 years (range 4-68 years)]. Majority of patients (76.5%) were below 40 years of age. Rheumatic heart disease (RHD) was the commonest underlying heart disease (present in 46.9% patients). Probable source of infection could be identified in only 16.6% episodes. None of their patients were intravenous drug abusers. Fever (90.0%), anemia (81.0%), clubbing (58.1%), splenomegaly (60.6%),new murmur (22.7%) were the common clinical findings. Vegetations were present in 89.9% episodes. Blood cultures were positive in 134 (67.7%) episodes (streptococci in 23.2%, staphylococci in 19.7%, gram negative in 13.6%, enterococci in 8.1%, polymicrobial and fungal in 1.5% episodes each). Complications were cardiovascular [congestive heart failure (CHF) in 41.9%, atrioventricular block in 1.5%, cardiac tamponade and acute myocardial infarction in 0.5% each), neurological in 16.6%, renal in 13.1% and embolisms in total 21.7% episodes. Total 21% patients died during therapy (cause of deaths; CHF in 11, septicemia in 10, cerebral embolism in 7, post cardiac surgery in 5, ruptured cerebral mycotic aneurysm in 2, ventricular tachycardia in 2 patients). On stepwise logistic regression analysis; cardiac abscess and CHF were independent predictors of cardiac surgery. Similarly, CHF, renal failure and prosthetic valve dysfunction were independent predictors of mortality

Modified Dukes criteria for diagnosis of Infective Endocarditis[4]

Defnite Infective endocarditis

Pathological criteria

Microorganisms : Demonstrated by culture or histology in a vegetation ,or in a vegetation that has embolized ,or in an intra cardiac abscess , or

Pathological lesions :Vegetation or intracardiac abscess present ,confirmed by histology showing active endocarditis

Clinical criteria ,using specific definitions listed below

Two major criteria,or

One major and three minor criteria, or

Five minor criteria

Criteria for Diagnosis of Infective Endocarditis

Major criteria

Positive blood culture

Typical microorganism for infective endocarditis from two separate blood cultures

Viridans streptococci ,Streptococcus bovis ,HACEK group or Staphylococcus aureus or community –acquired enterococci in the absence of a primary focus, or

Persistently positive blood culture ,defined as recovery of a microorganism

From Blood cultures(>/=2)drawn more than 12 hours apart,or

All of three or a majority of four or more separate blood cultures,with first and last drawn at least 1 hour apart

Single positive blood culture for Coxiella Burnetti or antiphase I IgG antibody titer>1:800

Evidence of endocardial involvement

Positive echocardiogram

Oscillating intracardiac mass ,on valve or supporting structures ,or in the path of regurgitant jets,or on implanted material ,in the absence of an alternative anatomical explanation or

Abscess ,or

New partial dehiscence of prosthetic valve ,or

New valvular regurgitation (increase in preexisting murmur is not sufficient)

Minor criteria

Predisposition –predisposing heart condition or intravenous drug use

Fever >/=38 degree Celsius

Vascular phenomenon :major arterial emboli, septic pulmonary emboli ,septic pulmonary infarcts,mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions

Immunological phenomenon : glomerulonephritis,Oslers nodes,Roth spots,rheumatoid factor

Microbiological evidence :Positive blood culture but not meeting major criterion as noted previously or serological evidence of active infection with organism consistent with infective endocarditis

Possible infective endocarditis

One major criterion and one minor criterion or three minor criteria

Rejected

Firm alternate diagnosis for manifestations of endocarditis ,or

Sustained resolution of manifestations of endocarditis with antibiotic therapy of 4 days or less

No pathological evidence of IE at surgery or autopsy,after antibiotic therapy for 4 days or less

Infective Endocarditis Chemoprophylaxis - Changes in guidelines [111]

In a major departure from previous AHA guidelines, the Committee no longer recommends IE prophylaxis based solely on an increased lifetime risk

of acquisition of IE. Patients with the conditions listed in Table 2, with a prosthetic cardiac valve, those with a previous episode of IE, and some patients with CHD are also among those patients with the highest lifetime risk of acquisition of endocarditis. No published data demonstrate convincingly that the administration of prophylactic antibiotics prevents IE associated with bacteremia from an invasive procedure.

The possibility that there may be an exceedingly small number of cases of IE that could be prevented by prophylactic antibiotics in patients who undergo an invasive procedure cannot be excluded. However, if prophylaxis is effective, such therapy should be restricted to those patients with the highest risk of adverse outcome from IE who would derive the greatest benefit from prevention of IE. In patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Table 2), IE prophylaxis for dental procedures are reasonable.

Table 2 . Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis for Which Prophylaxis With Dental Procedures Is Reasonable Class II a (LOE B)

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
*Congenital heart disease (CHD)**
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

AIMS OF THE STUDY

To study the clinical, microbiological spectrum, treatment and outcome of Infective Endocarditis treated in SCTIMST from January 2003 – August 2008 (over a period of 5 years and 8 months) .

MATERIALS AND METHODS

Data were collected on a retrospective basis from the clinical records of all patients who were admitted in this hospital with the diagnosis of Infective Endocarditis from January 2003 – August 2008. Only patients who met the Duke definitive or possible criteria for IE[3,4] were included. Data from clinical presentation, investigative work up and outcome was compiled and analyzed. Investigative work up in all patients included hemogram, urine examination, blood cultures, chest X-ray, electrocardiogram and echocardiography. Other investigations were done as and when required.

At least three blood samples for cultures (aerobic as well as anaerobic) were taken in all patients by three separate venipunctures at least 1 hour apart. Fungal blood cultures were done when thought necessary in native valve IE and in all cases of suspected prosthetic valve endocarditis. Transesophageal echocardiogram (TEE) was done in all patients with high clinical suspicion of IE but non-diagnostic transthoracic echocardiogram (TTE), all patients with suspected prosthetic valve endocarditis (PVE) and in all patients with suspected cardiac mechanical complications (abscess, valve perforation, acute/worsening valvular regurgitation).

Definitions

Vegetation - localized oscillating mass of dense shaggy echoes that was attached to a valve leaflet or to supporting structure or in the path of turbulent jet or on implanted material.[5]

Perivalvular abscess - defined as a region of reduced echo density or echolucent cavity adjacent to the valve or within the valvular annulus.[112]

Renal failure - serum creatinine of more than 1.5 mg/dl at presentation / during the course of treatment.

Relapse - recurrence within two months after completing treatment.

Recurrence - occurrence of more than one episode of infective endocarditis.

Prosthetic valve endocarditis was analyzed as a separate sub group.

Early PVE - occurrence within 2 months of surgery.

Intermediate PVE - occurrence within 2 months to one year.

Late PVE - occurrence more than one year after surgery .

Nosocomial endocarditis - hospital acquired endocarditis in a patient who underwent a recent intracardiac surgery or invasive diagnostic or therapeutic procedures.

Pathological evidence of IE was based on intra-operative appearance of affected area (valves and other structures) along with either demonstration of microorganism by microscopy/culture/histology or histological demonstration of active endocarditis in the vegetation/intracardiac abscess/valve or other cardiac tissue or embolic material.

Diagnosis of IE was made according to strict adherence to the Duke's criteria

STATISTICAL ANALYSIS

Data are expressed as mean ± SD. For comparing relation between variables and mortality and culture positive with culture negative episodes of IE; continuous variables were compared using ANOVA, while categorical variables were compared using cross tabs and test for significance of proportion. Stepwise logistic regression analysis was done to determine independent predictors for mortality in active IE. A p-value of <0.05 was considered as significant.

Results

147 patients satisfying inclusion criteria were identified and were analyzed. .

Age

Age ranged from 3.5 years to 68 years. Mean age was 34.65 years with a SD of 13.2 years. Majority of patients were in the age group of 30-39 years. There were 19 patients below 20 years and 20 patients above 50 years. Refer table 3.

Table 3 – Age group of patients

Age group	Number(%)
1-9	3(2.1%)
10-19	16(10.8%)
20-29	34(23%)
30-39	41(27%)
40-49	33 (22%)
50-59	13 (9%)
60-69	7 (4.8%)
Total	147 (100%)

Sex

Majority of patients were males 99(67.3%) with a sex ratio of 2:1.

Predisposing cardiac conditions

Rheumatic heart disease was the most common predisposing cardiac condition (36.8%), followed by prosthetic valve endocarditis (33.3%). Bicuspid aortic valve endocarditis accounted for 21 (14.3%) patients .Congenital heart disease (CHD) accounted for 6.8% only .The other studies from India[107] have included bicuspid aortic valve in CHD and hence their percentage of CHD was higher compared to this study.Refer table 4.

Table 4. Predisposing cardiac conditions for IE

Predisposing cardiac condition	Number(%)
Rheumatic heart disease (RHD)	54(36.8%)
Prosthetic Valve endocarditis (PVE)	49(33.3%)
Bicuspid aortic valve,AR (BAV)	21(14.3%)
Congential heart disease (CHD)	10(6.8%)
Mitral valve prolapse (MVP) ,MR	7(4.8%)
Hypertrophic cardiomyopathy,MR	1(0.68%)
Coronary artery disease ,MR	1 (0.68%)
Permanent pacemaker (PPI)	1(0.68%)
Tricuspid regurgitation (TR)	2(1.4%)
No structural heart disease (NSHD)	1(0.68%)
Total	147(100%)

MR= mitral regurgitation ,AR =aortic regurgitation,TR=Tricuspid regurgitation ,CHD congenital heart disease, PPI =Permanent pacemaker implantation.

Congenital heart diseases

Among the CHD,TOF was the most common predisposing factor but all of them were post operative infections. Refer table 5.

Table 5. Congenital heart diseases predisposing for IE

Congential heart disease n=10	n (%)
a. Tetrology of Fallot,Post ICR	4 (2.7%)
b. Single ventricle	1 (0.68%)
c. Ventricular septal defect ,AR	1(0.68%)
d. Mitral valve repair +ASD	1(0.68%)
e. VSD,Pulmonary atresia	2(1.4%)
f. VSD ,Tricuspid valve endocarditis	1(0.68%)

Intracardiac repair (ICR), Ventricular septal defect (VSD),Atrial septal defect (ASD)

Specific cardiac / valve lesions and Mortality

Prosthetic valve accounted for 49 cases (33.3%) and accounted for 26 deaths (48.1 %of the total mortality). Aortic regurgitation (AR)was the predisposing lesion in 22.4% of endocarditis. It accounted for 14 deaths (26.4%). The case fatality rate of aortic valve endocarditis was 42.4%. Mitral valve IE was present in 29 cases (19.7%) it caused 4 deaths (7.6% of mortality).The case fatality rate of mitral valve infective endocarditis was 13.8%, substantially lesser than that of aortic valve IE (p=0.03). Congenital heart disease predisposed to IE in 10(6.8%) cases. It accounted for 2 deaths (3.7%) of total mortality . The case fatality rate for CHD was 20% .Refer table 6.

Table 6.Frequency, Mortality,mortality percentage contributed by each lesion and mortality percentage in each valve/ cardiac lesions per se (case fatality rate) in infective endocarditis .

Predisposing lesion	Frequency. n=147(%)	Mortality n=54 (%)	Case fatality rate(%)
Prosth. Valve	49 (33.3%)	26 (48.1%)	53
AR	33 (22.4%)	14 (26.4%)	42.4
MR	29(19.7%)	4 (7.6%)	13.8
AR+MR	22(15%)	8 (15%)	36.4
TR	2(1.4%)	0	0
MS+MR	1(0.7%)	0	0
CHD	10 (6.8%)	2(3.7%)	20
PPI	1(0.7%)	0	0

MR= mitral regurgitation ,AR =aortic regurgitation,TR=Tricuspid regurgitation ,CHD congenital heart disease, PPI =Permanent pacemaker implantation,MS=Mitral stenosis .

Table 7. Organisms isolated in blood culture from patients with IE

Organisms isolated from blood culture	**Frequency(147) (%)**
Streptococci (Total)	19 (13%)
α hemolytic streptococci	17 (11.6%)
Other Streptococci	2 (1.4%)
Enterococci	14 (9.6%)
Staphylococci (Total)	21 (14.3%)
Coagulase negative staph aureus (CONS)	15 (10.3%)
Staph Aureus	5 (3.4%)
Methicillin resistant staph aureus (MRSA)	1 (0.7%)
Other Gram Positive cocci	2 (1.4%)
Diphtheroid	2 (1.4%)
Gram Negative	
Pseudomonas	2 (1.4%)
E Coli	2 (1.4%)
OtherGram Negative bacilli	3 (2.1%)
Acinetobacter	3 (2.1%)
Non Fermenters	2 (1.5%)
Micrococcus	1 (0.7%)
Fungal	13 (8.9%)
Candida	11 (7.5%)
Mixed infections	3 (2.1%)
Candida and enterococci	1 (0.7%)
Pseudomonas & nonfermenter	1 (0.7%)
Klebsiella and candida	1 (0.7%)
Culture negative	61 (41.8%)

Blood culture and sensitivity

Culture and sensitivity

Routine blood culture, sensitivity, and aerobic, anaerobic, fungal culture and sensitivity methods were done in all patients. Culture was negative in 61 patients (41.8%). Alpha hemolytic streptococci was grown in 17 patients (11.6%), Coagulase negative staph aureus was isolated in 15 patients (10.3%). Enterococci was isolated in 14 patients (9.6%) and Candida was isolated in 13 patients(8.9%). Mixed infections were seen in 3 patients. Refer table 7.The total number in culture exceeds the total number of patients due to mixed infection in 3 patients

Vegetation and size

Majority 129 (87.8%) had vegetation .Among them vegetation was more than 10 mm in size in (110) 74.8% patients. Refer table 8.

Table 8. Presence of vegetation and size .

Vegetation	Frequency (n=147)(%)
Vegetations present	129 (87.8)
>10 mm	110 (74.8)
<10 mm	19 (13)
No vegetations	18 (12.2)

Sources of bacteremia

The possible source of bacteremia are shown in the table 9. Majority did not have any any demonstrable sources of bactremia for causing infective endocarditis.

Table 9. Possible sources of bacteremia

Possible sources of bacteremia	Frequency(%)
Possible source of bacteremia- present	46 (31.3%)
Nosocomial	22 (14.9%)
Lower respiratoy tract infection	9 (6%)
Dental infections	5 (3.4%)
Sternal wound infection	3 (2%)
Prolonged ventillation and tracheostomy	2 (1.3%)
Urinary tract infection	2 (1.3%)
Skin infection	2 (1.3%)
Road traffic accident	1 (0.7%)
No demonstrable source	101 (68.7%)

Clinical Features

Fever -of the 147, 146 patients had fever at some point. Fever duration ranged from 2 days to 24 weeks(mean of 4.7 wks +/- 4.5wks).

Hepatomegaly and splenomegaly

Hepatomegaly was seen in 81(55%) patients and clinical splenomegaly was seen in 54 (36.6%) patients .Eight (5.4%)patients had sonological evidence of spleen enlargement without clinical splenomegaly .

Anemia (defined as hemoglobin less than 10 gm%) was observed seen in 109 (74%) patients .

Roth spots was seen in 14 (9.5%) patients

Total count The total count varied from 800-52200/mm^3 with a mean of 14788+/-7643 /mm^3 and the neutrophil count varied from 34% to 90% with a mean of 75%.Refer table 10.

Table 10. Total count (The highest count during the course of disease was taken)

Total count /mm^3	Frequency n=147(%)
< 5000	5 (3.4%)
5000-10,000	32 (21.8%)
10,000-20,000	84(57.1%)
20,000-30,000	18(12.2%)
30,000-40,000	6(4.1%)
>40,000	2(1.4%)

Complications

Most common cardiac complication was CHF present in 50 patients (34%). Thirty five patients (23.8%) did not have any complications. Renal failure was seen in 66 patients (44.9%). Valvular complications included para aortic abscess in 18 patients (12.2%), Valve perforation in 11 patients (7.5%), prosthetic valve dehiscence in 12 patients (8.2%).
Complications included CVA in 27 patients (14.3%), SAH in 8 patients (.4%), coronary embolism in 2 patients (1.4%), peripheral embolism in 21 patients (14.3%). Retinal artery occlusion and pneumatocele in the lung was seen in one patient each.

Organ complications seen were Renal failure in 66 patients (44.9%), CHF in 50 patients (34%), MODS was seen in 22 patients (15%), Sepsis in 22 patients (15%) .Most patients had more than one complications. Hence the total number exceeds the total number of patients. Refer table 11.

Table 11. Complications observed in infective endocarditis

Complications	**Frequency=147(%)**
Cardiac	
Heart failure	50 (34%)
Para aortic abscess	18 (12.2%)
Mitral annular abscess	5(3.4%)
Prosthetic valve dehiscence	12 (8.2%)
Paravalvar regurgitation	14 (9.5%)
Valve perforation	11 (7.5%)
Severe TR, Right heart failure	2 (1.4%)
Coronary embolism	2 (1.4%)
Aortic pseudoaneurysm	1 (0.7%)
Increased Prosth.valve gradient	1 (0.7%)
Renal failure	66 (44.9%)
Neurological	
1)CVA	27(18.4%)
2)Intracerebral Hemorrhage	10 (6.8%)
3)SAH	8 (5.4%)
Multisystem	
MODS	22 (15%)
Sepsis	22 (15%)
Peripheral Embolism	21 (14.3%)
Splenic abscess	3 (2%)
Digital gangrene	3 (2%)
Pneumatocele	1 (0.7%)
No complications	35 (23.8%)

Surgeries performed in patients with infective endocarditis

Surgery was done in 28 (19%) patients .AVR was done in 7 patients, MVR in 8 patients, DVR in one patient. Redo MVR was done in 2 patients, AVR and DVR in 3 patients each. One patient underwent PPI lead removal. Tricuspid valve repair was done in 2 patients and RVOT vegetation excision in one patient. Refer table 12.

Table 12. Surgeries performed in patients with infective endocarditis

Surgery	n=28
AVR	7
MVR	8
DVR	1
Redo AVR	3
Redo MVR	2
Redo DVR	3
PPI lead removal	1
RVOT vegt. excision	1
Tricuspid valve repair	2

Antibiotics

All patients were treated with appropriate antibiotics according to culture sensitivity reports and ACC/AHA recommendation. Culture negative patients were treated with ampicillin and gentmicin.Antifungal therapy was never given empirically.Most commonly used antibiotic was gentamicin (60 patients). Crystalline penicillin in 39 patients, Ceftriaxone in 26,ampicillin in 25 patients, Cloxacillin in 18, vancomycin in 15 patients, were among the many antibiotics used . Fungal IE was treated with amphotericin and

fluconazole. Rifampicin was used in 4 patients with prosthetic valve endocarditis.

Adverse reactions to antibiotics

Drug induced renal dysfunction was suspected in 22(15%) patients, neutropenia in 10 patients, penicillin allergy in 2 patients, drug induced fever in 3 patients. One patient had gentamicin induced cerebellar toxicity .

Follow up data

Follow up ranged from 6 months to 5 years (mean 2.1 yrs +/- 1.19 yrs).

Mortality

Fifty four patients expired during treatment (36.7%). Among those who expired during treatment 26 patients (48.1%) were having PVE. RHD and bicuspid aortic valve accounted for mortality in 11(20.4%) patients each Refer table 13.

Table 13. Mortality in relation to the predisposing condition and its contribution to the total mortality (%)

Predisposing factor	Frequency n=54 (%)
PVE	26 (48.1%)
RHD	11(20.4%)
Bicuspid AV	11(20.4%)
MVP	2 (3.7%)
VSD,PA	1 (1.9%)
TOF PO ICR	2 (3.7%)
ASD+MV repair	1 (1.9%)
NSHD	1 (1.9%)

Causes of mortality

The most common cause of mortality was heart failure seen in 20 patients (37%). Multi organ dysfunction syndrome (MODS) was the next common

cause of death . Overwhelming sepsis was the cause of death in 10 patients (18.5%),Intracerebral hemorrhage claimed 4 lives (7.4%) .Two patients died of myocardial infarction . Out of this one patient with native aortic valve endocarditis had a vegetation embolised to the left main coronary artery which was demonstrated by echocardiography .Refer table 14.

Table 14 . Causes of mortality among patients with IE

Cause of death	**Number n=54 (%)**
Heart failure	20 (37%)
Multi organ dysfunction syndrome	15 (27%)
Overwhelming sepsis	10(18.5%)
Intracerebral hemorrhage	4(7.4%)
Myocardial infarction	2(3.7%)
Adult respiratory distress syndrome	2 (3.7%)
Ventricular tachycardia	1(1.9%)

Univariate analysis of variables of all Infective endocarditis

In univariate analysis, progression of valve disease , CHF , Prosthetic valve endocarditis, splenomegaly, hepatomegaly, absence of surgical intervention in complicated IE ,elevated blood urea nitrogen, S creatinine ,elevated total count and neutrophilia were found to be predictive of mortality .(refer table 15)

Table 15. Univariate analysis of variables in relation to mortality in infective endocarditis (considering all cases).

	Survivors	**Percentage in survivors**	**Mortality**	**Percentage in mortality**	**P value**
Sex Males Females	63 30	67.4 32.6	36 18	66.7 33.3	0.187
Vegetation	86	93.5	47	87	0.000
Progression of valve disease	34	37	43	79.6	0.005
PVE	22/92	23.9	25/54	46.3	0.000
Anemia	59/91	64.8	50/54	92.6	0.002
Spleen	35/91	38.5	35/54	64.8	0.000
Heart failure	13/91	14.2	37/51	72.5	0.041
Stroke	14/91	15.4	16/54	29.6	0.177
Peripheral embolism	8/88	9.1	9/54	16.7	0.744
Culture positive	53/92	57.5	32/54	60.4	
Culture negative	39/92	42.4	21/54	39.6	0.004
Surgical treatment	30/92	32.6	6/54	11.1	0.000

Table 16. Univariate analysis of continuous variables in relation to mortality in infective endocarditis (Including all cases).

Variable		Mean +/-SD	95% CI		P value
			Lower	Upper	
Age (yrs)	Survivors	34+/-13.4	31.1	36.7	0.341
	Expired	36+/-12.7	32.7	40	
Fever duration(wk)	Survivors	5.4+/-5	4.3	6.5	0.271
	Expired	4.5+/-4.3	3.3	5.7	
ESR (mm/hr)	Survivors	73.7+/-30	67.2	80.3	0.235
	Expired	66.5+/- 37	55.2	77.7	
BUN (mg/dl)	Survivors	18.2+/- 14.7	14.8	21.6	0.000
	Expired	56.8+/-34.5	46.2	67.5	
S.creatinine (mg/dl)	Survivors	1.4+/-0.92	1.3	1.7	0.000
	Expired	3.3 +/-1.96	2.7	3.9	
TC (/mm^3)	Survivors	12297+/-4432	11941. 1	13913.8	0.000
	Expired	18098+/-10576	14920.	21275.4	
Neutrophis (%)	Survivors	72+/12	69.2	75.1	0.001
	Expired	79+/-10	76.7	83.3	

BUN-blood urea nitrogen,TC - total count,DC - differential count, ESR - erythrocyte sedimentation rate.

Multivariate analysis of total IE patients

In multivariate analysis , renal failure (p=0.008), Raised Blood urea nitrogen (=0.000), Serum creatinine (p=0.000) ,raised total count (p=0.001),differential count showing neutrophilia (p= 0.000) ,Prosthetic valve endocarditis(p=0.000), Prosthetic valve dysfunction (p=0.000) ,CHF (p=0.001), , and stroke (p=0.007) were found to have significant correlation with mortality . Refer table 17.

Table 17. Multivariate analysis of variables with relation to mortaltiy (Including all cases).

Parameter	p value
Elevated blood urea nitrogen	.000
Elevated S.Creatinine	.000
Surgical treatment	.001
Heart failure	.001
Prosth valve endocarditis	.007
Prosth valve dysfunction	.000
Stroke	.007
Elevted total count	.001
Neutrophilia	.000

PROSTHETIC VALVE ENDOCARDITIS (PVE)

Prosthetic valve endocarditis accounted for 49 patients (33.3%) in this study. Age of patients ranged from 13 to 65 years. Mean age was 40.3yrs (SD 11.7 yrs). Males were 27 (55 %) and females were 22 in number (45%)

Among the cases of prosthetic valve endocarditis majority were late PVE 23 patients (56.1%). There were 16 cases of early PVE (32.7%) and intermediate PVE was 10 patients (20.4%).Refer table 18.

Table 18. Timing of prosthetic valve endocarditis (PVE) .

Timing of PVE	Frequency n=49 (%)
Early	16 (32.7%)
Intermediate	10 (20.4%)
Late	23 (56.1%)

Clinical data

Pallor was present in 8 patients 17.4%.

Splenomegaly .Clinical evidence of splenomegaly was seen in 20 patients (44.9%) and sonological evidence of spleen enlargement without clinical splenomegaly was seen in in 10.2%.

Stroke Sixteen patients (34.8%) had CVA /TIA.

Roth Spots were present in 6 patients (12.2 %.).

Total Count ranged from 3000-52,200 cell/mm^3 (mean16,979 +/- 9710 cells/mm^3). Majority 57.1% had total count in the range of 10,000-20,000cells/mm^3.

Differential neutrophil count ranged from 58% - to 94% (mean 78% +/- 9%).

Clubbing was present in 33 patients (67.3 %).

Peripheral embolism was present in 5 patients (10.9%) .

Renal Failure

Renal failure was seen in 31 patients (63.2%) out of which drug induced renal dysfunction was suspected in 7 (14.3%). 18 patients (36.7%) had no renal failure. Refer table 19.

Table 19. Relation of valve replaced to the frequency of PVE.

Prosthesis	**Frequency n=49 (%)**
Aortic	11 (22.5 %)
Mitral	28 (57 %)
Aortic and mitral	10 (20.4 %)

Eleven patients had Aortic PVE . 28 patients had PVE of mitral prosthesis.

Ten patients had DVR and PVE.

Stroke in patients with Prosthetic Valve and PVE

Aortic PVE - 2 out of 11 (18 %) patients had stroke.

Mitral PVE - Nine out of 28 patients had stroke (33.3%) with a p value of 0.33.

Aortic and mitral - 5 patients in this group had stroke.

Early PVE

Sixteen patients had early PVE among which majority were caused by coagulase negative staph aureus (31.3%) and candida (25%). Gram negative bacilli, staph aureus, gram positive cocci and pseudomonas accounted for one case of early PVE each. Four were culture negative.Refer table 20.

Table 20 . Organisms grown in culture in early PVE

Culture	Frequency n = 16 (%)
CONS	5 (31.3%)
Gram positive cocci	1 (6.3%)
Diphtheroid	1 (6.3%)
Pseudomonas	1(6.3%)
Candida	4 (25%)
Culture negative	4 (25%)

CONS=Coagulase negative staphylococcus aureus

Intermediate PVE

Intermediate PVE consisted of 10 patients, 7 of which were caused by Candida and 2 by coagulase negative staph aureus. One patient had culture negative PVE. Refer table 21

Table 21 –Organisms grown in culture in intermediate PVE

Culture	Frequency n=10 (%)
Candida	7 (70%)
CONS	2 (20%)
Culture negative	1 (10%)

Late PVE

Late PVE was seen in 23 patients .Enterococci was the most common organism. Alpha hemolytic streptococci was isolated from 3 (13%) patients. 2 (8.7%) patients had CONS grown in culture. Candida was only seen in one patient that too as a mixed infection with enterococci . Refer table 22

Table 22- Organisms grown in culture in late PVE.

Culture	Frequency	Percentage
Enterococci	4 (17.4%)	17.4%
Enterococci and candida	1(4.4%)	4.4%
Alpha hemolytic strept	3 (13%)	13%
CONS	2 (8.7%)	8.7%
Staph aureus	1(4.4%)	4.4%
Pseudomonas and non fermenters	1 (4.4%)	4.4%
Culture negative	11 (47.8%)	47.8

Microbiology of PVE as a group.

Taking PVE together as a group, the most common organisms isolated were coagulase negative staph aureus and candida infections in 9 patients each (18.4%). Enterococcal infection was seen in 4 patients (8.2%). Alpha hemolytic streptococcal infection was seen in 3 patients (6.1%). Sixteen patients (32.7%) were culture negative. Refer table 23.

Table 23- Organisms grown in culture in PVE as a group

Organism	Frequency(49)	Percentage
Candida	9	18.4 %
Staphylococci		
CONS	9	18.4 %
Staph aureus	2	4.1%
Enterococcus	4	8.2 %
Alphahemolytic streptcocci	3	6.1 %
Gram positive cocci	1	2%
Pseudomonas	1	2 %
Gram negative		
Gram negative bacilli	1	2 %
Diphtheroid	1	2. %

Organisms	Frequency	Percentage
Mixed infections		
Candida and enterococcus	1	2. %
Pseudomonas and non fermenter	1	2. %
Culture Negative	16	32.7%
Total	49	100

Table 23(contd above) Organisms grown in culture in PVE as a group

Vegetations

33 patients (67.3 %) had vegetations more than 10 mm in size. Eight (16.3%) patients had vegetation of size less than 10mm. There were no vegetations in 8 (16.3%) patients. Refer table 24.

Table 24 . Vegetation characteristics in PVE

Vegetation characteristics	Frequency n=49 (%)
Vegetation Present	41 (83.7%)
Vegetation <10mm	8 (16.3%)
Vegetation >10 mm	33 (67.3%)
No vegetations	8 (16.3%)

TEE (trans esophageal echo) was done in 35 patients (71.5%).

Cure with Medical Treatment

Only 15 (30.6%) patients got cured with medical treatment only. The rest 34(59.4%) patients either expired or developed relapse or recurrence .

Surgical Treatment

Surgery was done in 8 patients (15.2%).

Outcome and Surgical treatment in PVE according to time of presentation

One patient each in early and intermediate PVE group expired inspite of surgery.

Re surgery

Re surgery was done in total of 8 patients out of 49(16%). 5 (31.3%) patients with early PVE underwent re surgery. Only 3 (30%) patients with Intermediate PVE underwent redo surgery. None of the patients with late PVE underwent re surgery.

Mortality

Mortality rate in those who underwent redo surgery (25%) was less than those in patients without surgery (63%) and this was statistically significant (p value =0.02). Mortality for early PVE was 7 patients out of 17 (41.2 %). Those with Intermediate PVE had a mortality of 6 out of 10 (60%). Mortality of 52% (12 patients) was seen in patients with Late PVE. Refer table 25.

Table 25 – Relation of timing of PVE, mortality and redo surgery

PVE	(n=49)(%)	Mortality	Redo Surgery
Early	n=16 (32.7%)	8 (50%)	5
Intermediate	n=10 (20.4%)	6(60%)	3
Late	n=23(56.1%)	12(52%)	0

Mortality in those with and without surgery

The results are shown in Table 26.

Table 26- Mortality in those with and without surgery

	Frequency n=49(%)	Mortality(%)
Without surgery	41 (83.7%)	26 (63%)
With surgery	8 (16.3%)	2 (25%)

New Valve lesion

New valve lesion was seen in 27 patients (58.7%).

Recurrence

Recurrence was seen in 4 (8.7%) patients with PVE. Recurrence after Re do was 1 out of 8 and with out surgery 3 of 41 had recurrence.

Relapse

One patient (2%) had relapse of PVE.

Mortality and Re do surgery

Aortic PVE -Three out of 11 (27%) patients with aortic valve endocarditis died. Redo surgery was done in 3 of 9 patients.

Mitral PVE- 18 of 28 patients with mitral PVE died (64.2%).

DVR PVE - 4 of 10 (40%) patients among this group died. 3 patients underwent redo DVR.

Mortality in mitral PVE was higher than the aortic PVE group(p=0.022)Refer table 27.

Table 27- Mortality and Re do surgery in PVE in relation to the valve replaced

Prosthesis	Number n=49 (%)	Mortality n=25 (%)	Re do n=8 (%)
Mitral	28 (57%)	18(72 %)	2 (7.1%)
Aortic	11 (22.5%)	3 (12 %)	3 (27.3%)
DVR	10 (20.4%)	4 (16 %)	3 (30%)

Univariate analysis of variables with mortality in patients with prosthetic valve endocarditis

A univariate analysis of different variables in relation to mortality was done in patients with prosthetic valve endocarditis .In this surgical treatment, progression of valve disease,anemia,heart failure, elevated blood urea nitrogen ,serum creatinine,total count and differential count were found to be significant predictors of mortality.

Table 28- Univariate analysis of variables in relation to mortality in prosthetic valve endocarditis

	Survivors	Percentage	Mortality	Percentage	P value
Males 27 Females 20	10 11	38.5 55	16 9	61.5 45	0.264
Vegetation	19/21	90	19/28	68	0.197
Surgical treatment	6/21	28.6	2/28	7	0.022
Progression of valve disease	8/21	38.1	20/28	71.4	0.022
Recurrence	1/21	4.8	3/25	12	0.385
Relapse	0/21	0	1/25	4	0.354
Fever	20/21	95.2	25/25	100	0.270
Anemia	15/21	71.4	23/28	82	.067
Splenomegaly	8/20	40	15/28	53.6	0.182
Heart Failure	3/21	14.3	21/28	75	0.000
Surgery	5/20	25%	1/25	4	0.039
Peripheral embolism	4/21	19	2/28	8	0.268
PV dysfunction	7/21	33.3	14/28	50	0.288
Clubbing	15/21	72.2	22/28	83.3	0.385
Culture positive	7/21	33.3	10/28	36	0.850
Culture negative	14/21	66.6	18/28	64	
CONS	4/21	19	2/28	8	0.268
Candida	3/21	14.3	6/28	20	0.611
Stroke	5/21	23.8	12/28	44	0.152

Table 29- Univariate analysis of variables in relation to mortality in prosthetic valve endocarditis

Variables	Category	Mean	+/-SD	p value
Age	Survivors	38.5	12.4	0.567
	Expired	40.4	11	
Fever duration	Survivors	5.2	5.9	0.293
	Expired	3.7	3.8	
ESR	Survivors	77.6	25.5	0.316
	Expired	70.2	22	
BUN	Survivors	15.7	5.8	0.000
	Expired	48.9	20.7	
S.Creatinine	Survivors	1.3	0.42	0.000
	Expired	3.4	1.7	
TC	Survivors	14330	4932	0.061
	Expired	20040	13000	
DC	Survivors	74.7	7.6	0.004
	Expired	82.5	8.9	

Table 30- Multivariate analysis of variables with relation to mortaltiy in prosthetic valve endocarditis

Variables	P value
BUN	0.001
S Creatinine	0.004
Re Do surgery	0.007
DC	0.002
CHF	0.025

In multivariate analysis, elevated blood urea nitrogen, serum creatinine, redo surgery, differential count and CHF were found to be independent predictors of mortality in prosthetic valve endocarditis.

Nosocomial endocarditis

Hospital acquired endocarditis was seen in 22 patients (14.9%).Sixteen patients had early PVE. Three patients had IE post op ICR for TOF. One patient had IE post op MV repair.Two patients had hospital aquired IE on native valve IE. Two patients out of the post OP ICR group expired. Eight out of the 16 patients in the early PVE group expired. Total mortality in the nosocomial IE group was 11 out of 22 (50%) patients. Re surgery was done in the patient who developed IE post MV repair but he expired. None of the patients of the post op TOF in this group underwent redo surgery. Two patients had native valve IE after hospital admissions for other causes. Redo surgery was done in 7(31%) patients in the nosocomial endocarditis group. Mortality rate in nosocomial IE was 50%.

Table 31- Nosocomial endocarditis -Predisposing factors ; re surgery; mortality rate and percentage

	Total n=22 (%)	**Mortality rate n=11(%)**	**Re surgery n=7**
Early PVE	16 (72.7%)	8 (72.3%)	5
Post ICR for TOF	3 (13.6%)	2 (18.4%)	0
Post MV repair	1 (4.5%)	1 (9.2%)	1
Native valve IE	2 (9.1%)	0	1

Fungal IE

Fungal IE was seen in 13 patients. Two patients has mixed infection (Candida +bacterial) .Nine of them were prosthetic valve related ,two were on native valve. Five were post MVR, three were post DVR and one case post AVR. Re surgery was done in 3 patients. One patient who underwent surgery expired later due to recurrence of IE and intracerebral hemorrhage. Eight patients (61.5%) had embolic complications. 5(38.5%) patients developed stroke. 4 patients had Intracranial hemorrhage. Six of the patients with fungal IE expired (46%).

DISCUSSION

Epidemiological factors

This study showed a male predominance (2:1). In the study by Eleftheiros Mylonkias et al the male to female ratio was 1.7:1[113] and in an Indian study by Garg et al it was 2.7:1.[107] The median age of patients with infective endocarditis was 30-40 years in the preantibiotic era and 47-69 years in the recent population[107]. In this study the mean age was 34.65 years +/- 13.2 yrs and majority of patients were in the age group of 30-39 years. This is in contrast to the west where majority of patients present beyond the fourth decade.[114,114] This could be due to the fact that RHD is common in our population and it affects much younger people. In the Indian study by Garg et al[109] mean age was 27.6±12.7 years and in the series by Choudhary et al[108] the mean age was 25 +/-12 years.

Predisposing cardiac/valve lesions (refer table 4)

Rheumatic heart disease was the major predisposing factor for infective endocarditis in this study seen in 50 patients (34%). This was followed closely by prosthetic valve endocarditis in 49 patients (33.3%). Bicuspid aortic valve was the underlying factor in 21 patients (14.3%). MVP was responsible only in 7 patients (4.8%). This is in contrast to the data from West where the most common predisposition for IE is MVP.[113] Other available data from India also show a high incidence of RHD and low incidence of MVP. PVE accounts for 7-25% of IE in most developed countries[115].

Source of bacteremia (refer Table 9)

Majority (68.7%) did not have any predisposing event producing bacteremia. Nosocomial endocarditis was seen in 14.9% .Dental infection predisposed to IE in 3.4%. A patient with recurrent PVE had dental abscess which could have predisposed to PVE. Some of the recent studies do not show any association between dental procedure and IE.[115] Prolonged ventilation, tracheostomy (1.3%) and sternal wound infection (2%)

were some of the predisposing factors in prosthetic valve endocarditis. The study by Rajib Choudhary et al[108] showed that abortal and puerperal sepsis were precipitating factors of IE ,but this was not seen in our study. The incidence of Right sided IE due to drug abuse is increasing in the West but this is not the case in Indian series. None of our patients with right or left sided IE had history of intravenous (IV) drug abuse. In the Garg series[109] (198 patients) also there were no patients with history of IV drug abuse . Choudhury et al reports one patient with history of IV drug abuse.[108]

Microorganisms (refer Table 7)

Culture positivity was observed in 86 (58.2%) patients. Blood cultures have been reported to be positive in more than 90.0% patients of IE in western series. This is higher than many previous Indian studies, which have reported culture positivity in 21–47% episodes.[110,116,117,118,119]The Garg series[109] reported a culture positivity 66% - the maximum among Indian studies.

Culture was negative in 61 patients (41.8%).The high prevalence of culture negative endocarditis compared to western series[113] could be due to the fact that most patients were initially treated elsewhere with antibiotics. Failure to culture could also be due to inadequate microbiological techniques. The Indian study by Rajib Choudhary et al[108] reported 54% culture negativity. According to current literature, only 5 to 7 % of patients who have been given a diagnosis of infective endocarditis according to strict criteria and who have not recently received antibiotics will have sterile blood culture.[120] In the study by Garg et al[109], the incidence of culture negativity was 32.3%. In a recent series[121], 63 cases of blood culture negative infective endocarditis (BCNIE) were studied, in which previous antibiotic treatment had been administered in half of the patients. In another significant group of patients with culture negative IE , blood cultures were negative because of difficulty in isolating certain microorganisms. In another more recent series, (the largest study on culture negativity till date)[122] among 348 cases of culture negative IE, 167 (48%) were associated with C burnetii, 99 (28%) with Bartonella species, and 5 (1%) with rare, fastidious agents of endocarditis. Among 73 cases without aetiology, 58 received antibiotic treatment before blood cultures. In

this study prior antibiotic treatment and unavailability of immunological methods for identifying the causative organisms could have resulted in high prevalence of culture negativity.

In this study staphylococcus (total) was grown in 14.3%, streptococcus (total) in 13% ,alpha hemolytic streptococci was the most frequent organism grown in culture (11.6%). Coagulase negative staph aureus(10.3%),enterococci (9.6%) and Candida (8.8%) and mixed infections (2%) were the organisms isolated .

In the study by Garg et al the most common organism isolated was streptococcus (23.2%). Staphylococci (19.7%) ,enterococci (8.1%) and gram negative organisms (27%) and fungal IE (1.5%) were isolated in that study. The higher incidence of fungal IE in the present study may be due to higher incidence of prosthetic valve endocarditis.

Vegetations (refer Table 8)

Vegetations were present in majority of patients (90%). Vegetations were picked up by TTE in majority of patients (n = 104, 70.7%).Trans oesophageal echocardiogram was performed in 81 patients (55.1%) .TEE picked up vegetations in 25(17%) patients which were missed by TTE. TEE was very helpful in diagnosing complications of IE (especially in PVE) like paravalvar /paraaortic abscess , vegetations on prosthetic valve etc.

The specificity of TTE in picking up vegetation is 98%, however it may be inadequate in upto 20% of patients with a specificity for vegetation of only 60-70%.[123] Sensitivity for detection of vegetations of TEE is 75-95% maintaining a specificity of 85 to 98 % .[124,125] Vegetations of more than 10 mm in size was seen in 110(74.8%) patients whereas vegetations were less than 10 mm in size in 19 patients (13%). Single vegetation was seen in 90 (61.2%) patients, multiple vegetations were seen in 39(26.5%) patients. 4 patients had vegetations on tricuspid valve, 4 patients had vegetations on the patch /RVOT after surgical repair of TOF. One patient had IE on the permanent pacemaker lead .2 patients had vegetation on the aortic valve in VSD pulmonary atresia.

In the study by Naveen Garg[109], vegetations were observed in 89.9% episodes,single vegetation was more common than multiple vegetations (66.7% vs. 23.2%)and vegetations of <10 mm and >10 mm size were nearly equally distributed (46.5% and 43.4% episodes) respectively

Natural history of vegetations

Vegetations persisted as such in 83 patients (62.9%).Vegetations disappeared during /after treatment in 23 cases (17.4%). They increased in size in 26 cases (19.7%) .Cedric Vuille et al in their study on natural history of vegetations during treatment of IE showed that 59% had no change in size during treatment and 22% disappeared during treatment.[126]

Complications (refer Table 11)

Congestive heart failure and neurologic events have the greatest influence on the prognosis of infective endocarditis .

Cardiac complications (refer table 11)

The most common complication in this study was CHF, which was noticed in 50 patients (34%) .Heart failure can occur up to 55% of patients with IE. It is the one of the most common cause of death in patients with IE. In the SGPGI series cardiac failure was seen in 41.9% of patients.

The usual cause of congestive heart failure in patients with infective endocarditis is infection-induced valvular damage. Aortic-valve infection is more frequently associated with congestive heart failure than is mitral-valve infection.[122] Extension of infective endocarditis beyond the valve annulus predicts higher mortality, the more frequent development of congestive heart failure, and the need for cardiac surgery.

In this study, native aortic valve endocarditis had a more incidence of paravalvular abscess,more stroke and more mortality than native mitral valve endocarditis (p value 0.022). The two cases of ACS that occurred were also related to

aortic valve endocarditis. Periannular extension of infection occurs in 10-40% of patients with native valve IE and complicates aortic IE more commonly than mitral IE[122]. It predicts higher mortality and frequent development of heart failure. In this series ,paraaortic abscess was seen in 18 patients (12.2%) and mitral annular abscess was seen in 5 (3.4%) patients. This might be the true incidence of paravalvar abscess in this population because this complication was specifically looked for during TTE and TEE was done whenever it was suspected. TEE was done in 55% of patients. However if TEE was routinely performed in all patients it could have picked more cases of perivalvar abscess. In Garg et al [109] series paravalvar abscess was reported in 7% patients only probably because of underutilisation of TEE.

Systemic embolism (refer table 11)

In this study the incidence of systemic embolism was 44.8% (66 patients). Systemic embolism was another reason for morbidity. According to Arnold Bayer et al[120], systemic embolism occurs in 22-50% cases of IE. Most common site of embolism is CNS, 65% of all embolisms involved the CNS[43].

Neurological manifestations (refer table 11)

The total incidence of CNS involvement was about 30.2% in this study . Neurologic complications develop in 20 to 40 percent of all patients with infective endocarditis.[127,128] In the SGPGI series CVA occurred in 12% patients and mycotic aneurysm in 3%. Embolic CVA occurred in 18.4% patients . Intracerebral hemorrhage was seen in 6.8% and SAH in 5.4% of patients in this study.

Mycotic aneurysms

Mycotic aneurysms are uncommon complications of IE. They occur in 1.5-5% of cases, most commonly involves intracranial arteries.[122] The mortality rate among those with mycotic aneurysms is reported to be about 60%.[122] In this study 6(4.1%) patients had mycotic aneurysms but remarkably all of them survived. 5 of them had intracerebral mycotic aneurysms and bleeding and one had multiple mycotic aneurysms in the peripheries. Two of the 5 patients with intracerebral

mycotic aneurysms underwent aneurysmectomy. Out of the mycotic aneurysms 5 were related to native valve IE (4 mitral and 1 aortic valve IE) and one was related to prosthetic aortic valve IE.

The rate of embolic events in patients with Infective endocarditis decreases rapidly after the initiation of effective antibiotic therapy, from 13 per 1000 patient-days during the first week of therapy to fewer than 1.2 per 1000 patient-days after two weeks of therapy.[101,129,130,129] In this study also most of the embolic events occurred during the initial period at presentation or before starting of antibiotics.

Systemic Emboli and Splenic Abscess (refer table 11)

Peripheral embolism was noted in 21 (14%) patients. The most common site of embolism in peripheries were the anterior tibial and dorsalis pedis artery. Digital gangrene was seen in 3 (2%) patients . One patient had brachial embolism and gangrene of hand. Systemic embolism is a frequent complication of Infective endocarditis and most commonly involves the spleen, the kidney, the liver, and the iliac or mesenteric arteries. The incidence of peripheral embolism was 4% in the study by Garg et al . Splenic abscess may develop from bacteremic seeding of a previously infarcted area or direct seeding of the spleen by an infected embolus. Splenic abscess was seen in 3 patients (2%).

Renal dysfunction (refer table 11)

Renal dysfunction was seen in 44.9 % (66 patients). Cause of renal dysfunction was suspected to be drug induced in 22 patients. Immune complex glomerulonephritis with nephritic syndrome was seen in 4 cases. Renal dysfunction was part of multiorgan dysfunction syndrome in majority of cases. In the study by Majumdar et al renal dysfunction was seen in 40-50% of their patients.[130]

Relapse

Relapse was seen in 14 patients (9.5%). Relapse of infective endocarditis usually occurs within two months of the discontinuation of antimicrobial therapy. The relapse rate for patients with native-valve endocarditis caused by penicillin-susceptible streptococcus viridans who have been treated with one of the recommended courses of therapy is generally less than 2%. The relapse rate for patients with enterococcal native-valve endocarditis after standard therapy is 8 to 20 %. Among patients with infective endocarditis caused by Staph. aureus, Enterobacteriaceae, or fungi treatment failure often occurs during the primary course of therapy and relapse of infection may be an indication for combined medical and surgical therapy.[113]

Clinical course of patients with IE(refer table 12)

Cardiac surgery was done in 28 (19%) patients. Commonest indications for surgery were worsening/refractory CHF [in 15 (53.6%) patients]. Other indications were persistent infection despite adequate antibiotic therapy, prosthetic valve dysfunction, intra cardiac abscess and recurrent embolization. Total in-hospital mortality of patients who underwent surgery was 14.2% (4 out of 28 patients).Total in-hospital mortality of active IE in this study was 36.7% (54 out of 147 patients). Refractory cardiac failure was the commonest cause of death (37 %). In the Garg series also cardiac failure was the commonest cause of death .[109]

Sub group analysis

Subgroup analysis was done between culture positive and culture negative group with reference to occurrence of complications. Intracardiac complications, systemic organ dysfunction, embolism and CHF were compared between the two groups. No significant difference was seen. Comparison between streptococcal IE and non streptococcal IE did not show significant difference in occurrence of complications or mortality. Analysis of patients who died versus who recovered showed that prosthetic

valve IE, CHF, paravalvar and root abscess ,renal failure were predictors of mortality from IE.

Outcome and analysis of predictors of mortality (ref tables 15,16,17)

Mortality rate in IE depends on multiple factors like causative organisms and presence of complications. Western studies have shown a consistent decline in the mortality of IE and are currently reported between 15.0–33.0%.[15,114,116] Similar trends have been shown in Indian studies; 42.0% in 1970[118], 20.3% in 1981[119], 21.0–25.0% in 1992[108,121]and 13.9% in 1998.[110] In this study mortality was seen in 36.7% of patients. Total in-hospital mortality in present study was much higher and is explained by the differences in the study population. Ours is a tertiary care center, receiving relatively refractory and complicated cases. Mortality is 2-3 times higher in tertiary level centers than in community hospitals.[131]Mortality is high in this study due to referral bias in tertiary care institute. Besides the high number of prosthetic and nosocomial IE is also a reason for the high percentage of mortality. In the present study, independent predictors of mortality were CHF, renal failure and PVE, similar to those reported by Siddiq et al.[132] Besides in this study stroke, prosthetic valve endocarditis, neutrophilia and elevated total count were also predictors of mortality. Several other predictors have been reported in other studies. Chaudhury et al[108] reported significantly higher number of neurological complications in patients who died compared with those who recovered. Jaffe et al[133]reported PVE, systemic embolism and infection with staphylococcus aureus as independent predictors of death. Similarly in a recent study, neurological symptoms on admission, arthralgia and weight loss were strong independent predictors of increased mortality.[112]

Recent studies have suggested that mortality can be reduced by surgical interventions, more so in patients who presented with CHF.[135,134,135,136] In fact studies in which cardiac surgery was done in large number of patients, CHF was not an independent predictor of mortality.[112,133] Surgery in IE is uncommonly reported in

Indian series.[108,110,119-121]In the present series, cardiac surgery was done in 19% episodes with acceptable results. Commonest indication for surgery was refractory CHF. In the series by Garg et al, despite cardiac surgery in 23% episodes, commonest cause of death remained CHF. This further suggests that many more deaths could have been prevented by early cardiac surgery in these patients.

Prosthetic valve endocarditis

Prosthetic valve endocarditis accounted for 49 (33.3%) patients in this study. The mortality rate in PVE was 53%. Only 8(16%) patients underwent re surgery among them. Mortality rate was 25% in this group whereas in the group managed with medical treatment, the mortality rate was 63.4%. According to the current literature, the mortality rate is 33-45% with lower mortality rate in late PVE.[137] The improved survival in PVE in recent series is due to more number of patients undergoing early surgical intervention.[88] The high mortality in this study can be explained by lesser number of patients with complicated PVE who underwent surgery.

Sixteen (32.7%) had early PVE, 10 (20.4%) had intermediate PVE and 23 (56.1%) patients had late PVE. Mitral prosthesis was involved (57%) more often than aortic prosthesis(22.5%).The incidence of stroke in mitral prosthesis was more compared to the aortic prosthesis (33.3% vs 18%). Mortality in mitral PVE was higher than the aortic PVE group (64.2% vs 27%) (p=0.022). Mortality in the early, intermediate and late PVE group were high but relatively similar (50-60%), but the paradoxical least mortality in the early PVE group could be explained by the fact that more patients in this group underwent re surgery whereas no patients in the late PVE underwent surgery.

The current relapse rate in prosthetic-valve endocarditis is approximately 10 to 15 percent. The relapse rate for PVE was 4 patients (8.2%) in this study which is consistent with other studies.

Prosthetic mitral valve endocarditis was not only more in frequency than the prosthetic aortic valve IE but also the frequency of complications and mortality were

more in this group (p value 0.02). The statistically significant predictors of mortality from PVE were renal failure, prosthetic valve dysfunction,absence of surgical intervention, and neutrophilia.

Nosocomial endocarditis

Nosocomial endocarditis was seen in 22 patients with a mortality rate of 50% . The prognosis for nosocomial native valve endocarditis is worse than other forms of native valve IE. Mortality rate may be up to 50%[138] .This may be due to more virulent and antibiotic resistant organisms and also due to more invasive nature of infection.

There has been a reduction of mortality in IE during the last two decades from 30% to 10-20%, which may be due to more complicated invasive infections with abscess and aneurysms and prosthetic valve infections.[82] The significant reduction in mortality with early surgical intervention in this study proves this point.

Limitations of the study

1. Retrospective nature of the study.

2.The high percentage of culture negative endocarditis prevented the correct identification of microbiological spectrum.

3.Culture negativity poses a significant diagnostic dilemma especially when echocardiogram fails to demonstrate vegetations.

Conclusions

1. Spectrum of IE in our country is different from the West, but quite similar as reported from developing countries about 40 years ago.
2. It occurs in relatively younger population and RHD is the commonest underlying heart disease.
3. Infective endocarditis in MVP, degenerative heart disease and intravenous drug abusers is uncommonly seen.
4. Streptococci are still the commonest microorganisms responsible for IE.
5. Infective endocarditis still has high morbidity and mortality.
6. Prosthetic valve IE is one of the common types of IE seen in this geographical locality and it carries significant mortality.
7. Prolonged ventilation, sternal wound infections and tracheostomy are risk factors for PVE.
8. Early Redo surgery in complicated PVE with CHF due to valvar insufficiency, complicated invasive infections with paravalvar abscess and aneurysms and PVE not responding to treatment helps to improve survival.
9. Predictors for mortality were local intracardiac complications, CHF, prosthetic valve dysfunction, renal failure, stroke, absence of surgical treatment, multiorgan dysfunction syndrome, elevated total count and neutrophilia.
10. Native aortic valve endocarditis resulted in more local complications and mortality than native mitral valve endocarditis.
11. Mortality associated with prosthetic mitral valve endocarditis was more than that seen with prosthetic aortic valve.
12. Outcome is better with early surgery in patients with decompensation and heart failure.

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Project 2

Sytemic venous anomalies – Clinical, Morphological and Electrocardiographic Correlations

INTRODUCTION

A wide variety of abnormalities can occur in systemic venous return, some of these have little physiologic significance and others produce cyanosis. Two well known anomalies of the systemic veins are persistent left superior vena cava (PLSVC) and infra hepatic interruption of the inferior vena cava (IVC) with azygous continuation. Rarely either persistent left SVC or interrupted IVC drains into the LA producing cyanosis.

Improvements in the diagnosis and treatment of cardiovascular disorders have brought these anomalies to the attention of cardiologists and cardiac surgeons. Some of these abnormalities produce difficulties in the manipulation of catheters during cardiac catheterization and preoperative knowledge of systemic venous anomalies is important in cardiac surgery. Therefore the search for common abnormalities of the systemic veins has become routine in the evaluation of pediatric cardiac patients during echo and cardiac catheterization.

The studies available about LSVC are all related to the prevalence of LSVC in the general population or those undergoing pacemaker implantation. There are no studies which are done with LSVC as the primary abnormality. Hence this study was undertaken to know the mode of presentation of patients with venous anomalies, associated congenital heart disease and analyze the electrocardiographic findings and conduction disorders in these patients.

REVIEW OF LITERATURE

SYSTEMIC VENOUS ANOMALIES

The word vein stems from the latin verb *venio* meaning "to come". Hence the vein is a passage, a conduit, a vessel which carries blood to the heart regardless of the consistency of the blood it carries.

The spectrum of systemic venous anomalies varies widely from minor asymptomatic anatomic variations to complex abnormalities that lead to cyanosis or that might complicate surgical repair of congenital heart disease.Systemic venous anomalies are classified as shown in Table 1.

Table 1. **Classification of systemic venous anomalies**

Areas affected	**Anomalies**
Superior caval veins	**Left superior caval vein to right atrium:** bilateral superior caval veins,absent right superior caval vein,left superior caval vein with localized coronary sinus defect **LSVC to LA** **Levoatrial cardinal vein** **Right SVC to LA** **SVC accepting pulmonary veins** **Aneurysm of SVC**
Inferior caval veins	**Absence of the infrahepatic segment of the IVC with azygous continuation** **IVC to left atrium** **IVC accepting pulmonary veins** **Miscellaneous anomalies of the IVC**
Coronary sinus **Systemic veins : TAPVC** **Valves of the embryonic venous sinus**	

ANOMALIES OF SUPERIOR VENA CAVA

Variants of the left superior caval vein draining to the systemic venous return are:

1.Left superior caval vein to right atrium:

i)Bilateral Superior Caval Veins

A left sided superior caval vein draining to the coronary sinus is the most common systemic venous anomaly. It results from persistence of the left superior cardinal vein. [1] This lesion has been noted in 0.3% of autopsies in general population (Geissler and Albert ,1956)[2,3] but occurs in 2-4.4% of patients with congenital heart disease(Campbell and Deuchar ,1954 ;Fraser et al ,1961,Cha and Khoury,1972)[4,5,6] . Descriptions of persistent LSVC dates back to 1787.[7] The persistent left SVC is connected to the right atrium in 92% of cases and to the left atrium in the remainder producing cyanosis.[8]

ii)Persistent left superior venecava draining into right atrium

In the most common type, the left SVC is connected to the coronary sinus. A left superior caval vein usually co exists with a right sided superior caval vein. A brachiocephalic vein connects these two structures in three-fifth of these patients. Its size varies with inversely with that of the left vein (Winter 1954)[9]. The left vein is located anteriorly to both the aortic arch and the left pulmonary artery. It then passes inferiorly, accepts the inferior caval vein ,descends medially into the posterior atrioventricular groove and runs into the coronary sinus, passing between the left pulmonary veins and the left atrial appendage.

The presence of left SVC does not usually affect the cardiac hemodynamics.It is often noted as an incidental finding in cardiac catheterization. Certain clinical findings may suggest its presence .

Colman (1967)[10] described the presence of excessive venous pulsations on the left side as a clinical clue. Chest radiographs may suggest the diagnosis if a left superior paramediastinal 'crescent' of water density is present (Cha and Khoury, 1972)[6]. Electrocardiograms show a leftward P wave axis in 35% (Momma and Linde, 1969)[11] to 70% (Hancock 1964) [12]of patients. This abnormal P wave axis has been referred to as 'coronary sinus rhythm' (Scherf and Haris, 1946; Hancock 1964) [12,13] and may be a result of persistence of left sided embryonic pacemaker tissue (Patten 1956).[14]

It more likely indicates that the patient has unrecognized left atrial isomerism. The enlarged coronary sinus may be the first clue to the presence of this anomaly .A brachiocephalic vein should always be looked for routinely during cardiac catheterization .Its absence is highly suggestive of the presence of a left superior caval vein. If the left atrium is visualized during the course of angiography, a dilated coronary sinus may cause an unusual indentation on its inferior border (Owen and Urquhart 1979).[15]

The presence of a left superior caval vein may make difficult or impossible cardiac catheterization or transvenous insertion of a pacemaker lead if the approach is from the left arm. At the time of an open heart procedure, a left superior caval vein may be managed by temporary occlusion or by ligation,if the venous pressure proximal to the clamp does not rise above 30 mmHg(de Leval et al ,1975) [16].Alternatively the vessel may need direct cannulation,usually through the right atrium and coronary sinus. Zerbe et al (1992) [17] have designed a technique of placement of permanent pacemaker leads through a PLSVC by reshaping the end of the lead into pig tail configuration. In addition to coronary sinus rhythm,investigators have noted the co existence of fatal arrhythmias and pre excitation in some patients with a persistent LSVC(James et al 1976).[18] Davis et al 1981 reported that the prevalence of preexcitation is 10 times greater in patients with PLSVC than in general population.Although the PLSVC has no direct consequences

concerning the mode of drainage of the systemic venous return; its presence has recently been shown to be of more concern. Cochrane et al (1994)[19] described patients in whom PLSVC pinged in the vestibule of the mitral valve producing obstruction to the left ventricular inflow, which was alleviated when the vein was surgically plicated. Support of this finding was then provided by Agnoletti and colleagues (1999)[20] who discovered an increased incidence of left sided obstructive lesions in patients with PLSVC.

Isolated persistent left SVC does not produce symptoms or signs. Cardiac examination is entirely normal. Chest X ray films may show the shadow of the left SVC along the upper left border of the mediastinum. The enlarged coronary sinus may be imaged by an echo study.

The diagnosis is suspected from two dimensional studies, and angiocardiography confirms the diagnosis. Treatment of isolated persistent left SVC is not necessary. There are only few studies in the prevalence in patients with symptomatic bradyarrhythmias requiring permanent cardiac pacing. In the study by Biffi et al[21] there was a slightly higher prevalence of LSVC persistence compared to general population; but this may be viewed as lower than what is expected, given the association with abnormalities of impulse formation and conduction.[22,23,24,25,26,27] The finding of a LSVC complicating placement of left-sided pacemaker or implantable cardiac defibrillator systems has been reported as a sporadic observation in literature, mainly in isolated patients. Of a total of 661 patients undergoing VVI-mode PM system implantation, Zerbe et al [28] reported 4 patients with LSVC persistence, but the observation was retrospective and no systematic attempt to assess the prevalence of this abnormality by consecutive left-sided approach to each PM implantation was made.

Practical implications Permanent pacemaker implantation - Different techniques have been used to obtain a reliable position of the implanted

pacemaker lead in these patients,[13,29,30,31,32] minimizing exposure to radiation and risk of lead dislodgment.[14,15] Many authors found helpful ways to shape stylets as to enter the tricuspid valve or to reach the right atrial appendage.[13,17] Active fixation leads were used to ensure lead stability,[33,34] although this was not mandatory in all the cases.

In patients with difficult positioning of the pacemaker lead through the coronary sinus, a right approach is recommended after visualization of a right vena cava entering the right atrium by echocardiography[35] or contrast venography; the absence of RSVC would suggest an epicardial implantation.[36] Biffi et al [21] suggests that implantation be accomplished left sided when diagnosis is made intraoperatively, unless catheter handling appears difficult or fluoroscopy time exceeds a defined maximum. Relevant implications of the above observation may apply to the fields of critical care, anesthesiology, general and thoracic surgery, oncology, and hematology when central lines for monitoring or therapeutic purposes are required[30,37] or when permanent catheters for drug delivery are implanted.

Awareness of this venous anomaly may obviate unnecessary catheter removal and troublesome placement of a new one when arterial puncture is suspected by imaging techniques, but not obvious at bedside verification tests. In addition, assessment of the RSVC may be very important in these patients, since its absence may represent a major obstacle in providing care of critical patients.

Persistence of LSVC has been associated with atrial arrhythmias, atrial fibrillation, sick sinus syndrome and complete heart block. Ablation of site in the LSVC has been reported to cure atrial fibrillation. Bass SP et al reports a case of four-year-old girl who suffered a cardiac arrest due to complete heart block without ventricular escape, during the flushing of an errantly placed long term central venous catheter. It was subsequently found that the central line

was placed in a persistent left superior vena cava (LSVC) draining directly into the coronary sinus.[38] The clinical significance of a persistent LSVC has also been recognized by cardiac surgeons when cannulating the heart for cardiopulmonary bypass or performing the Mustard procedure for correction of transposition of great arteries. Venous anomalies are extremely important when planning surgery for congenital heart diseases requiring univentricular repair. Retrograde cardioplegia through a persistent LSVC may lead to inadequate myocardial perfusion and therefore be ineffective.[39] The interruption of persistent LSVC during cardiac surgery in patients with coronary sinus ostial atresia, may lead to severe myocardial ischemia.[40]

LSVC has an implication in AVNRT .The slow atrioventricular nodal pathway is usually situated close to the coronary sinus os. Difficulties in ablation of the slow pathway has been reported , presumably the very large coronary sinus os reduces the distance between the fast and slow pathways and this made selective ablation of one pathway difficult.[33]

iii)Absent right superior caval vein

Complete absence of the right superior caval vein occurs occasionally in the presence of a left vein draining into the coronary sinus. In this situation, the left vein receives a right sided brachiocephalic vein. The right SVC may be then represented by a vestigial fibrous cord in the anatomical specimen (Karnegis et al 1964)[41].This anomaly results from complete involution of the right superior cardinal vein .The incidence of this anomaly is 0.1% of patients undergoing cardiac catheterization. Clinical diagnosis may be suggested if the chest radiograph shows absence of the right parasternal shadow of the right SVC. Cross sectional echocardiography should clearly demonstrate this anomaly if careful suprasternal imaging of the systemic veins is performed. Arrhythmias are not uncommon in this condition. They include atrioventricular block,ventricular ectopy,atrial fibrillation and sinus nodal dysfunction (Camm

et al 1979[42],Lenox et al 1980[43]).If a permanent pacemaker is required, an implanted epicardial system is generally preferred .

At open heart surgery the left superior caval vein should be cannulated carefully to avoid damage to the coronary sinus, which could cause post operative arrhythmias. Ligation of the left sided superior caval vein must be avoided (de Leval et al 1975[44];Lenox et al 1980[43]).

iv)Left superior caval vein with interatrial communication through the mouth of the coronary sinus

A window between the left atrium and the coronary sinus is a rare anomaly and is usually associated with persistence of the LSVC(McCotter,1916 ;Mankin and Burchell 1953;de Leval et al 1975;Lee and Sade 1979).[44,45,46,47] A spectrum of deficiencies can result from maldevelopment in this region .A localized defect simply produced partial unroofing of the coronary sinus ,causing it to communicate to the left atrium .If the deficiency is more marked, the left vein is directed to the left atrium ,near the appendage. This is usually associated with an interatrial communication at the anticipated position of the coronary sinus .Such a localised deficiency of the wall of the coronary sinus found in association with the left superior caval vein draining to the left atrium, may be associated with a physiological left to right shunt to the right atrium .This may produce physical findings consistent with an atrial septal defect ,but would be usually be dominated by the clinical findings of the associated congenital heart defects .During cardio pulmonary bypass ,the presence of oxygenated blood draining from the coronary sinus suggests the possibility of this anomaly (Lee and Sade 1979)[47].

2.Persistent Left Superior Venecava draining into left atrium

Rarely (8% of cases), persistent left SVC drains into the LA, resulting in systemic arterial desaturation. This is due to failure of invagination between

the left sinus horn and LA; therefore the coronary sinus is absent. Associated cardiac anomalies almost invariably are present. Complex defects, such as cor biloculare, conotruncal abnormalities and asplenia syndrome are commonly found. Defects of the atrial septum, single atrium, secundum ASD, primum ASD are also frequently found.

Clinical manifestations are dominated by the associated complex cardiac defects. In the absence of complex defects, cyanosis is more marked when there is no atrial communication, than when there is an ASD.

Surgical correction is necessary. When there is an adequate sized bridging vein that connects two SVCs, simple ligation of left SVC is performed. If the right SVC is absent or a bridging vein is inadequate, the left SVC is transposed to the RA. There is a risk of paradoxical systemic embolism in cases of LSVC drainage into the LA

Occasionally, a PLSVC can be misdiagnosed as descending thoracic aorta, however, it can be differentiated from the descending thoracic aorta by pulse-wave Doppler assessment that shows continuous flow in the PLSVC and pulsatile flow in the descending thoracic aorta. The diagnosis of PLSVC (draining to RA through the CS) is classically made by injecting contrast into the left-sided brachiocephalic veins and demonstrating contrast appearance in the PLSVC, CS, and RA (in that sequence). In 10% of patients, a PLSVC may drain into the LA either directly or via an unroofed CS; in such a situation, contrast first appears in the LA. Because of the PLSVC draining into the LA (right to left shunt), the arterial blood gas analysis or pulse oximetry will show desaturation.

Rarely PLSVC may connect to the pulmonary veins and has reported to cause desaturation and transient ischemic attacks. Recto M R [48]reports about a patient with PLSVC connected to the pulmonary veins who developed two episodes of transient ischemic attacks following flushing of an IV line placed

in the left hand. They also report successful closure of PLSVC by amplatzer vascular plug.

3.Levoatrial cardinal vein

It was Edwards and DuShane (1950) [49] who first described an anomalous venous connection, between the left atrium and the left brachiocephalic vein in a patient with mitral atresia. They termed this vessel the levo atrial cardinal vein. It is thought to represent persistence of the early connections between the pulmonary venous and cardinal venous systems in the setting of pulmonary venous obstruction .It differs from a persistent left superior caval vein in that it ascends dorsal to the left pulmonary artery. These channels are rare abnormalities found when the clinical presentation is dominated by the association with atrioventricular valvar atresia or hypoplastic left heart syndrome. Anderson [50] describes this anomaly in the absence of left sided atrioventricular valvar atresia.

4.Right superior caval vein draining into the left atrium

Anomalous drainage of the RSVC to the left atrium has been rarely reported as an associated anomaly. It is said to result from misalignment of the right horn of venous sinus in a leftward and cephalic direction .As a result the dominant superior caval vein connects to the left rather than the right atrium (Kirsch et al 1961)[50] .There is a right to left shunt of approximately one third of systemic venous return (Kirsch et al 1961)[50] and patients are usually cyanotic. The degree of desaturation may be so mild that the patients escape diagnosis until adulthood .They have normal auscultatory findings but often have ECG evidence of left ventricular hypertrophy and mild polycythemia consistent with chronic systemic desaturation .Cross sectional echocardiography could also be used to make this diagnosis with injection of contrast in the arm vein demonstrating the abnormal connection. If catheterization is performed an approach from the arm is necessary to visualize this anomaly angiographically.

Complete surgical correction has been achieved either by anastomosing the anomalous vein to the right atrium (Kirsch et al 1961)[50] or by diversion of caval venous blood flow to the right atrium using a pericardial patch.

5.Superior caval vein receiving pulmonary veins

Anomalous pulmonary venous connection to a right or left sided superior caval vein may occur as a result of persistence of anastomotic channels between the pulmonary venous and cardinal venous system.

6.Aneurysm of the superior caval vein

Discrete areas of dilatation of the superior cava vein may occur as isolated abnormalities in asymptomatic patients .Most aneurysms of the superior caval vein have been described in adults Yokomise (1990)[51] described a 13 year old boy with large aneurysm of the superior caval and brachiocephalic veins .Surgical resection was undertaken to prevent the theoretical possibility of formation of thrombus and pulmonary embolism .The diagnosis of a caval venous aneurysm is usually made after a routine chest radiograph demonstrates an incidental finding of a right sided anterosuperior mediastinal mass .There is usually no evidence of tracheal compression .The mass may be larger when the patient is lying supine.

ANOMALIES OF THE INFERIOR CAVAL VEINS

1.Absence of the hepatic segment of the inferior caval vein with azygous continuation The most common venous anomaly involving the inferior caval vein is absence of its infrahepatic segment with azygous continuation to the superior caval vein. The dilated azygous system serves as the major channel of systemic venous return from the lower half of the body. Only the hepatic veins continue to drain to the right atrium. This defect results from failure of the right subcardinal vein to develop properly and to anastomose with the right

vitelline vein, leading to enlargement of the right supracardinal vein, which provides continuation of systemic venous return to the developing superior caval vein.

Azygous continuation is seen in 0.6% of patients with congenital heart disease (Anderson et al 1961)[52].It is frequently associated with complex cyanotic lesions and bears a strong association with left isomerism (polysplenia syndrome)(Freedom and Ellison ,1973;Sharma et al 1987). [47,53] Roguin and colleagues (1989)[54] reported a case in which there was bilateral azygous continuation from the inferior caval vein to both right and left superior caval veins. In the setting of isomerism, the hepatic venous connections are usually direct to the atriums although it is possible to have hepatic venous connections to a persistent inferior venecaval vein co existing with azygous continuation of part of the venous return from the lower body (Guenthard et al 1990).[55] Strictly speaking the anomalous vein in those with left isomerism is a hemiazygous vein, but it is convenient to term it the azygous vein. The enlarged vein may be visible in the frontal chest radiograph as a prominent rounded structure of water density in the right upper perihilar region. Absence of the usual inferior venecava on a lateral view may also aid in the diagnosis as long as a film is obtained with good inspiration and the patient does not have marked increase in pulmonary vascular markings. Electrocardiograms have been noted to show coronary sinus rhythm or leftward superior P wave axis in a large percentage of those patients who also had left isomerism (Polysplenia syndrome)(Freedom and Ellison 1973)[47].Garcia et al (1981) [56] reported 6 patients with absence of inferior caval vein with left isomerism who developed complete heart block. The diagnosis of azygous continuation of the inferior caval vein is easily made with cross-sectional echocardiography (Huhta et al 1984)[57].The presence of this anomaly makes cardiac catheterisation from the lower extremity more difficult, but it can usually be accomplished using a balloon catheter. When the caval vein is cannulated at the time of open heart surgery, care must be taken

that the tip of the cannula lies on the cardiac side of the entrance of the azygous vein. The hepatic veins can usually be cannulated as a single vessel (de Leval et al 1975).[44] The major significance of this anomaly lies in the association with complex cardiac defects, and in the technical difficulty that can accompany cardiac catheterisation .

Vijayvergiya[58] et al reports a case of interrupted IVC with azygous continuation associated with sick sinus syndrome which needed permanent pacemaker implantation.

Patients with polysplenia have a leftward and superiorly oriented p wave axis in leads 2, 3, aVF and upright p waves in I and aVL. The initial tracing in V6 was positive. The frontal P wave axis varied from -50° to -80° in all patients prior to digoxin administration. The PR interval corrected for age and rate was normal in all instances. In all patients for whom there were serial electrocardiographic records, the records showed transition from one ectopic focus to another .An occasional patient even showed variation from coronary sinus rhythm to nodal rhythm in the same tracing. Freedom et al suspected digoxin toxicity in the patients on digoxin therapy, but even when digitalis was stopped for several days,the nodal rhythm would persist. The mean frontal QRS axis appeared leftward and superior in five patients and the QRS inscription was counterclockwise and superior. In the remainder, the mean QRS axis was either in the normal range or showed abnormal right axis deviation.

The differentiation of coronary sinus rhythm from left atrial rhythm is often difficult and the electrocardiographic P wave changes often overlap in these rhythms.[59] Although a diagnosis of coronary sinus rhythm is made from a leftward and superior P wave axis, it has been shown that the origin of this rhythm may be in the inferior left atrium, [2,60] bundle of His,[61] or lower right atrium ,including the orifice of the coronary sinus [2,3] . Lau and co workers [2]

have paced the inferior left atrium in close proximity to the coronary sinus and have produced P wave and P loop changes which were indistinguishable form those of coronary sinus rhythm .In addition ,inversion of the P wave in V6,thought to be almost diagnostic of left atrial rhythm ,[62] was consistently noted by these authors both in coronary sinus an left atrial pacing .Based in these observations ,Lau and colleagues [2] suggested that a common intra atrial conduction pathway is utilised in the genesis of both coronary sinus and left atrial rhythm.

In a review of all electrocardiographic records from 30 patients with the congenital asplenia syndrome on whom autopsies were performed at The Childrens Hospital Medical Center yielded only one patient with coronary sinus rhythm.[63] Momma and Linde[64] did not document coronary sinus rhythm in their six asplenia patients,but rather found a vertical and inferior P wave axis. Ruttenerg and his collegues [65] make no mention of abnormalities of atrial rhythm in their clinico- pathological review of 17 patients with the asplenia syndrome. Ongley and his associates[66] noted inverted P waves in inferior leads in polysplenia. There may be sinoatrial conduction tissue adjacent to the left superior venecava –left atrial junction.[67] . In this, left sided conduction tissue becomes the dominant atrial pacemaker, as it did in Van mierops report[68] . The frontal P wave vector should be directed from left to right and inferiorly suggesting atrial inversion, not leftward and superiorly as in coronary sinus rhythm.

Absence of superior portion of the inferior venecavae is very common in polysplenia and is quite rare in asplenia than polysplenia, although asplenia and absent inferior venecavae may rarely coexist.[69] Perhaps this abnormality of the sinus venosus either directly or indirectly affects the development of the right sided sino atrial node, predisposing to ectopic and possibly a more primitive atrial rhythm. This speculation does not explain those instances of coronary sinus rhythm when there are no abnormalities of the sinus venosus. A

normal inferior venecava may be present in polysplenia. [70] .Momma and Linde [74] and Jue and Edwards [71] have described patients with typical polysplenia rhythm but with a normal inferior venecavae. Their patients showed coronary sinus rhythm, although Jue and Edwards [81] referred to the P wave abnormality as "an ectopic right atrial pacemaker".

Absence of the renal to hepatic portion of the inferior venecavae with either an azygous or hemiazygous extension not infrequently makes cardiac catheterization from leg difficult, if not impossible.[72] Axillary approach has been used in patients in whom inguinal approach failed.

2.Inferior caval vein connected to the left atrium.

A small number of case reports exist of connection of the inferior caval vein to the left atrium,both with an intact atrial septum (Gardner and Cole 1955 [73]; Meadows 1961) [74]and with an atrial septal defect (Kim et al 1971) [75]. A distinction must be made between direct connection to the left atrium and an arrangement in which inferior caval vein overrides a low lying interatrial communication and allows functional drainage of IVC flow to the left atrium.

This lesion leads to an obligatory right to left shunt similar to that seen with superior caval venous connection to the left atrium. Patients are usually cyanotic with associated nail bed clubbing and polycythemia. Electrocardiograms may be normal or show left ventricular hypertrophy and left atrial enlargement. The chest radiograph may not be diagnostic. A definitive diagnosis can be made by cardiac catheterization with angiograph but had also been demonstrated with contrast echocardiography and MRI (Meyers et al 1989)[76]. These patients may survive into adult life with minimal symptoms but they are prone to paradoxical embolisation.The defect is amenable to surgical repair (Black et al 1964, Kim et al 1971).[66,77]

4.Inferior caval vein accepting pulmonary veins Totally anomalous pulmonary venous connection below the diaphragm is a well known entity .Partial connection of the pulmonary veins to the IVC also occurs. This is frequently associated with Scimitar syndrome .This developmental complex initially descried by Neill et al (1960) [78]consists of hypoplasia of the right lung ,anomalous systemic arterial supply to part of the right lung, a right sided heart and anomalous pulmonary venous connection from the right lung through a Scimitar vein to the region of the junction of right atrium and IVC.Mardini et al [79](1981))described a patient with anomalous left pulmonary venous connection to the IVC associated with hypoplasia of the left lung .They considered this an example of left sided Scimitar syndrome.

3.Miscellaneous Anomalies of the Inferior caval vein

These include duplication of the inferior caval vein below the level of the renal veins, left sided inferior caval vein and circumaortic renal collar. They have no hemodynamic significance, but may be of importance when surgical procedures are necessary in the retroperitoneal area (Downey et al 1990).[80]

The hepatic veins normally connect to the IVC, but they have been reported to connect directly to the right atrium through a separate orifice in a patient with partial atrioventricular septal defect and separate right and left atrioventricular valves. (de Leval et al 1975).

Many of these anomalies are incidental findings with very little hemodynamic significance. Their importance lies in the fact that they complicate cardiac catheterization, interventions and surgical procedures and may be associated with more important congenital cardiac anomalies. They may be associated with conduction system anomalies as well.

AIMS OF THE STUDY

This study was undertaken with the following objectives:

1. To determine the age of presentation and mode of presentation of patients with congenital heart disease associated with venous anomalies.
2. To analyze the associated cardiac defects in patients with venous anomalies.
3. To analyze the ECG findings in these patients and to delineate the ECG correlations with these anomalies.
4. To analyze the abnormalities in conduction system /rhythm occurring in these patients as detected by electrocardiography.

MATERIALS AND METHODS

This study is a retrospective study. A computer search of the medical records of all patients admitted during the period from January 2003 till June 2008 was done for venous anomalies. Patients with venous anomalies were identified by perusal of echocardiographic, cardiac catheterization/MRI records and surgical notes . Statistic was done with SPSS 15 software values are expressed as mean +/ - standard deviation. P value <.05 was considered significant.

PATIENT SELECTION

Inclusion criteria

All patients (outpatients and inpatients) with venous anomalies evaluated at SCTIMST during the period from January 2003 till June 2008.

Exclusion criteria

1. Patients of venous anomalies with incomplete medical records.
2. Situs inversus totalis with normal mirror image systemic venous drainage were excluded.

METHODOLOGY

A retrospective analysis of the clinical, electrocardiographic, echocardiographic and hemodynamic data of these patients were done. Analysis of patients with persistent Left superior venecava and interrupted inferior venecava were done separately. There were 55 patients with interrupted IVC and 106 patients with PLSVC. The clinical data was complete in 46 patients with interrupted IVC and 91 patients with PLSVC. (Total of 137 patients).

RESULTS

PLSVC group

Ninety one patients had persistence of the left SVC as the only systemic venous anomaly.

Age

Age ranged from 1 day to 65 years. Mean age at presentation was 15.2 years with SD of 16.2.

Sex

Fifty one (56%) were males and forty (44%) were females .

Presenting symptoms

Cyanosis was the presenting symptom in 34 % patients, incidental detection of heart disease in 30 patients, DOE in 30 patients and Syncope in 3 patients.

Cyanotic vs Acyanotic heart disease

Thirty five (38.5%) patients had cyanotic heart disease and Fifty six (61.5%) had acyanotic heart disease.

Diagnosis

Heart diseases seen in Left SVC group were atrial septal defect (ASD) in 29 patients , ventricular septal defect (VSD) in 13 ,Single ventricle in 3,tetrology of Fallot (TOF) in 12 patients, Double outlet right ventricle (DORV) in 5 ,Pulmonary atresia in 4,Common atrium in 2, Complete atrioventricular septal defect (AVSD) in 2 ,L transposition of great arteries (L TGA), Total anomalous pulmonary venous drainage (TAPVC)and D TGA were seen in one patient each and Bicuspid aortic valve with Aortic stenosis

(AS) in 3 patients . There were no structural heart diseases (NSHD) in 8 patients.The results are shown in Table 2 below.

Table 2: Underlying heart diseases seen in the persistent LSVC group (Patients with bilateral SVC).

Diagnosis		Frequency (n =91) (%)
ASD (n=29) (31.9%)	OS	**16 (17.5%)**
	SV	**12(13.2%)**
	OP	**1 (1.1%)**
VSD		**13 (14.3%)**
TOF		**12 (13.2%)**
DORV		**5 (5.5%)**
Pulmonary atresia		**4 (4.4%)**
Single ventricle		**3 (3.3%)**
Bicupid AV,AS		**3 (3.3%)**
Cor triatriatum		**2 (2.2%)**
Common atrium		**2 (2.2%)**
Common AVV valve		**2 (2.2%)**
RHD,MR		**2 (2.2%)**
D -TGA		**1 (1.1%)**
C-TGA		**1 (1.1%)**
PS+ MS		**1 (1.1%)**
Tricuspid atresia		**2 (2.2%)**
TAPVC		**1 (1.1%)**
NSHD		**8 (8.8%)**

(SV=Sinus venosus,OP=Ostium primum ,OS=ostium secundum,ASD= atrial septal defect)

Situs

Situs was solitus with d loop levocardia seen in 85(93.4%) patients. Situs solitus dextrocardia was seen in 2 (2.2%) patients and situs inversus levocardia was noted in 3 (3.3%) patients ,situs ambigus was seen in one patient.(1.1%)

Bilateral superior venecava (SVC) and isolated LSVC

Bilateral SVC was seen in 84 (92.3%) patients. Isolated LSVC (with absent RSVC) was seen in 7 patients (7.7%) patients.

LSVC size

LSVC was large in 82 patients (90.1%) and small in size in 9 patients. Of the patients with small LSVC , 2 had left axis deviation of P wave.

PV drainage

Normal Pulmonary venous drainage was seen in 73 (80.2%) patients. Partial anomalous venous drainage (PAPVC) was seen in 15 (16.5%) patients and TAPVC was seen in 3 (3.3%) patients.

ELECTROCARDIOGRAPHY

P wave axis

P axis varied between –165° to +135° with a mean of +33.3° and a SD of 43.2°.

P axis was normal in majority 51 (56%) patients .Left axis deviation of P wave was seen in 31 patients (34%) , Right axis deviation of P wave in 8 (8.8 %) patients ,and north west axis was seen in one patient (1.1%) .Refer Table 3.

Table 3- P wave axis in patients with persistent LSVC group (Patients with bilateral SVC).

P Wave axis	n=91	Percentage
Left axis	31	34%
Normal	51	56%
Right axis	8	8.8 %
North west axis	1	1.1

PR Interval

The PR interval varied between 80-280ms with a mean of 135.8 ms and SD of 40.6 .PR interval was less than 100 ms in one patient only .Majority 62.6% (57 patients) had PR interval between 100-160 ms .

Twenty one patients (23.1%) had PR interval between 160-200 ms. Twelve patients (13.2%) had PR interval more than 200 ms . Refer Table 4.

Table 4-PR interval in persistent LSVC group (Patients with bilateral SVC).

PR interval	Frequency	Percentage
<100	1	1.1
100-160	57	62.6
160-200	21	23.1
>200	12	13.2

Junctional Rhythm

Eleven patients had junctional rhythm.

QRS axis

Left axis deviation of QRS was seen in 15 patients . Normal QRS axis was seen in 47 patients, right axis deviation of QRS in 23 patients, extreme right axis was seen in 4 patients . QRS axis corresponded to the underlying cardiac abnormality.

Varying rhythm

8 (8.8%) patients had unstable rhythm varying between sinus and junctional rhythm.

Permanent pacemaker implantation

6 patients underwent PPI out of which 4 were for Sick sinus syndrome and 2 were for CHB.

Rhythm abnormalities

Of the patients with LSVC, 3 patients had atrial flutter and one patient had atrial tachycardia. Four patients underwent pacemaker implantation for sick sinus syndrome and 2 patients for CHB. Of the three patients with SSS ,two had concomitant AV nodal disease also . Two patients had sinus pauses of approximately 2 sec, that did not warrant PPI.

Analysis of Isolated LSVC group (with absent RSVC)

This group included 7 patients.

The age group ranged from 2-44 years. Mean age was12.83 years.

One patient had SSS and atrial flutter with pauses > 3sec.

Situs was normal in four patients.

Situs inversus levocardia was seen in 2 patients.

Pulmonary venous drainage was normal in all patients.

Left axis deviation of P wave was seen in 1 patient , 3 patients had normal P axis ,One patient had extreme axis deviation of P wave .

One patient had SSS with Atrial flutter and underwent Pacemaker implantation.

Analysis of interrupted IVC with azygous continuation

Forty-six patients had Interrupted IVC.

Age ranged from 1 day to 31 years with mean of 8.2 years

24 were males (52.2 %) and 22 were females (47.8%).

Presenting symptoms

Cyanosis was the presenting symptom in 29 patients (63%) ,Dyspnea on exertion in 17 patients 36.9%, recurrent respiratory tract infections in 14 (30%)patients, congestive heart failure and failure to thrive in 7 patients (15%)

Acyanotic versus cyanotic heart disease

Majority 29 patients (63%) were associated with congenital cyanotic heart disease and 17 patients (37%) were acyanotic heart disease. Refer Table 5

Table 5- Cyanotic versus acyanotic heart disease in patients with interrupted IVC

Heart disease	N=46 (%)
Cyanotic	29 (63%)
Acyanotic	17 (37%)

Associated cardiac defects

DORV was seen in 10 patients (21.7%) , Single ventricle in 7 patients (15.2%) , VSD was seen in 6 patients (13%) , AVCD in 5 patients (10.9%) , OS ASD and common atrium in 3 patients each (6.5%) ,OP ASD ,Pulmonary atresia and combination of tricuspid and pulmonary atresia was seen in 2 patients each.

Table 6- Associated cardiac defects in patients with interrupted IVC

Cardiac defects	Frequency n=46) (%)
DORV	10 (21.7%)
SV	7 (15.2%)
VSD	6 (13%)
Complete AVCD	5 (10.9%)
OS ASD	3 (6.5%)
Common atrium	3 (6.5%)
OP ASD	2 (4.4%)
PA	2 (4.4%)
TA and PA	2 (4.4%)
RHD,MS	1 (2.2%)
AVCD with TOF	1(2.2%)
Valvar PS	1 (2.2%)
DCRV	1 (2.2%)
PDA	1 (2.2%)
HLHS	1 (2.2%)

AV canal defects

Eleven patients (23.9%) had abnormality of the atrioventricular septum (AVCD). Common atrium was seen in 3 patients. Ostium primum ASD was seen in 2 (4.4%) patients ,Complete AVCD was seen in 5 patients (10.9%) ,one patient had TOF with AV canal defect.

Cardiac malpositions

Left isomerism and Situs ambigus was seen in 10 patients each (21.7%). Normal situs with d loop was seen in 18 patients (39.1%), situs inversus dextrocardia was seen in 3 patients (6.5%), situs inversus mesocardia was seen in 2 patients (4.3%) . Refer Table 7.

Table 7 – Malpositions associated with the interrupted IVC

Malposition	Frequency n=46 (%)
Situs solitus levocardia	18 (39.1%)
Left isomerism	10 (21.7%)
Situs ambigus	10 (21.7%)
Situs inversus dextrocardia	3 (6.5%)
Situs inversus mesocardia	2 (4.3%)
Situs solitus dextrocardia	1 (2.2%)
Situs inversus levocardia	1 (2.2%)
Situs ambigus dextrocardia	1 (2.2%)

17 out of 46 patients had malposed great vessels (36.9 %). 8 out of 46 (17.4%) had l- malposed aorta 5 (10.9%) had d- malposed aorta 4 (8.7%) had side by side great arteries .

Sinus rhythm

Only 3 (6.5%) patients out of 46 had normal P wave axis.

P axis

P axis in patients with Interruption of IVC varied between -180° to +120° with a mean of – 33.1° and SD of 63.6°.

Axis of P wave

Left axis deviation of P wave was seen in 34 patients (73.9%) , Extreme axis deviation of p wave was seen in 5 patients (10.9%) , normal P axis was seen in 3 patients only (6.5%) and right axis deviation of p wave was seen in 4 patients (8.7%).Refer table 9.

Table 9- P wave axis in patients with interrupted IVC

P axis	Frequency=46 (%)
Left axis	34 (73.9%)
Extreme axis	5 (10.9%)
Normal	3 (6.5%)
Right axis	4 (8.7%)

Varying P axis

P wave varying between one focus to another was seen in 11 patients (23.9 %)

PR interval in patients with interrupted IVC

Sixteen (34.8%) had PR interval less than 100 msec. Normal PR interval was seen in majority 26 (56.5%)patients out of which 22 patients (47.8%) had PR interval between 100-160. First degree heart block was seen in 4 patients. Refer table 10.

Table 10- PR interval in patients with interrupted IVC

PR interval	Frequency	Percentage
80-100 ms	16	34.8
100-160 ms	22	47.8
160-200 ms	4	8.7
>200 ms	4	8.7

QRS axis

Left axis deviation of QRS was seen in 4 patients (8.7 %). 5 patients had north west QRS axis (10.9 %). 31 patients had normal QRS axis (67.4%) . 6(13%) patients had Right axis deviation of QRS axis. QRS axis was concordant with the underlying cardiac problem. Refer table 11.

Table 11- QRS axis in patients with interrupted IVC

QRS Axis	Frequency	Percentage
Left axis	4	8.7
Normal	31	67.4
Right axis	6	13
Extreme axis	5	10.9

Junctional Rhythm

Intermittent Junctional rhythm was seen in 10 patients (21.7%)

Varying Rhythm

10 patients (21.7%) had intermittent junctional rhythm or ectopic atrial rhythm.

Left atrial or right atrial enlargement

Four patients had left atrial enlargement and 3 patients had right atrial enlargement.

Analysis for persistence of LSVC in patients with interrupted IVC

Out of the 46 patients with interrupted IVC , majority 30 patients (65.2%) had PLSVC (bilateral SVC) .Situs solitus dextrocardia with mirror image normal superior venecavae were excluded from the analysis for PLSVC

Bilateral SVC versus Unilateral SVC

Bilateral SVC was seen in 26 patients (56.5%). Isolated PLSVC was present in 4 patients (8.7%).

DISCUSSION

Persistent LSVC

The studies available about LSVC are all related to the prevalence of LSVC in the general population or those undergoing pacemaker implantation. There are no studies which are done with LSVC as the primary abnormality.

In this study the most common underlying heart disease seen in Left SVC group (refer table 2) was ASD which was seen in 31 (34.1%) patients. ASD is a common association of PLSVC .As explained by John Marshall[81] LSVC is usually obliterated in the early extra uterine life due to the compression between the hilum of left lung and left atrium. In conditions like ASD and mitral atresia, less compressive forces are present to obliterate the LSVC and it tends to become patent. Mitral atresia was not found in the LSVC group in this study. In absent RSVC, it is obligatory for the LSVC to remain patent.

Aortic arch hypoplasia or coarctation was not observed in the study. This is in strong contrast to a fetal echocardiographic study done by L Pasquini who observed that LSVC is a strong indicator of coarctation of aorta.

Bilateral SVC was seen in 84 (92.3%) patients. Isolated LSVC was seen in 7 patients (7.7%). This is in agreement with the literature where LSVC as the sole SVC forms less than 10% cases of PLSVC, the majority having bilateral SVC. Absence of the right-sided superior vena cava is rarer with an incidence of 0.07- 0.13%[82,83] in the general population .The findings in the study differ from that reported by Biffi, where the incidence of isolated LSVC was 33% .[2,21,84]

Majority (56.5 %) had a normal PR interval. Normal P axis was seen in majority (56%) of the patients. Left axis deviation of P wave with normal PR interval was seen in 31 patients (34%). Hancock[12] reported a high prevalence of leftward P axis with a normal PR interval, in PLSVC but its significance is not clear.

In contrast to the patients with interrupted IVC, the LSVC group had more incidence of first degree heart block (12 patients –13%).

Rhythm abnormalities

2 (2.2%) patients had atrial fibrillation, one (1.1%) had atrial flutter and one patient (1.1%) had atrial tachycardia. Hwang et al postulated that initiating ectopics from the LSVC are arising from ectopic pacemaker cells. [85]Ablation in the LSVC has been reported to cure the arrythmia[85] several recent studies demonstrated that the ligament of Marshall, which contains the vein of Marshall, is important in arrhythmogenesis through its muscle sleeves which continue into the coronary sinus forming an inferior inter-atrial pathway.[85]

Developmental abnormalities leading to a persistent LSVC are associated with abnormalities of cardiac conduction and ectopic pacemaker cells.[86,87].Exercise induced AF may also be seen in patients with LSVC.

Pacemaker implantation was done 6.6% patients with PLSVC. Out of which four were for sick sinus syndrome and 2 patients for CHB. Of the three patients with SSS, two had concomitant AV nodal disease also. Two patients had sinus pauses of approximately 2 sec that did not warrant PPI.

In the study by Biffi et al [21],in patients undergoing pacemaker implantation, they observed a similar, although slightly higher, prevalence of LSVC persistence compared to general population but they opined that it is

lower than what is expected given the association with abnormalities of impulse formation and conduction. [22,23,24,25,27, 88]

The persistent LSVC is associated with anatomical and architectural abnormalities of the pacemaker and conduction tissues. Both AV node and sinus node can show persistent fetal dispersion in the central fibrous body in subjects with persistent LSVC.

Patients with LSVC have an abnormal alignment of the AV node the AV node being more vertical. Dilatation of the CS and stretching of AV node is another mode of involvement of the conduction system.[36]

Isolated LSVC (With absent right SVC) was seen in 7 patients (7.6%) In this study 1 patient with isolated LSVC had SSS with Atrial flutter and underwent Pacemaker implantation. Sinus node dysfunction needing pacemaker had been reported in patients with isolated LSVC. [22]

Interrupted IVC

There is no previous study of patients with systemic venous anomalies as the primary abnormality. Most of the reported cases of IVC interruption in the literature are confined to pathological series of left atrial isomerism or polysplenia.

Although azygous continuation of the IVC can occur in isolation, this anomaly can co-exist with relatively simple congenital cardiac anomalies. However it is most frequently associated with the complex congenital cardiac anomalies associated with polysplenia.

In this study, polysplenia was identified in 10 (21.7%) cases (by echocardiography combined with ultrasound abdomen, during surgery and on

fluoroscopy), and situs ambigus in 10 patients .Almost all earlier series of left isomerism were based on pathological studies on heart specimens. The low incidence of polysplenia compared to that reported by Stella Van Pragh et al (75%) could be due to the purely clinical nature of the study that could have underasessed the proportion of patients with polysplenia .[89]

Zuberbuhler et al [53] studied the morphology of 22 autopsied hearts (out of 1842 hearts from the cardio pathological museum of children's hospital of Pittsburgh) diagnosed to have bilateral left sidedness based upon the morphology of the atrial appendages . There was infrahepatic IVC interruption with azygous continuation in 18 cases (82%).This stresses the point that IVC interruption is an almost invariable accompaniment of left atrial isomerism. The pulmonary veins connected bilaterally to the respective atrial chamber in 11 hearts (50%).

The interatrial septum was variably deficient in 20 of 22 hearts (91%). In 8 (36%) the atrial septum was severely attenuated and only a "crest " was presented . In 2 hearts the atrial septum was represented only by a strand .This is in comparison with 30% association of IVC interruption with common atrium in our study.

Bilateral SVC was seen in 26 patients (56.5%) in our study. This is in concordance with Zuberbuhler et al [53] who had an incidence of bilateral SVC of 59%.

In this study, left isomerism and Situs ambigus was seen in 10 patients each (21.7%). Situs solitus levocardia was seen in 18 patients (39.1%), situs inversus dextrocardia was seen in 3 patients (6.5%), situs inversus mesocardia was seen in 2 patients (4.3%).

Zuberbuhler et al [53] reported levocardia in 14 cases (64%), dextrocardia in 5 (23%), and mesocardia in 3 cases (13%).

In our study 11 (23.9%) had AV canal defects. Complete AV canal defect was seen in 5 patients and partial AV canal defect in 6 patients. In the Zuberbuhler series [53], fifteen hearts had a biventricular and ambiguous AV connections. Of these 14 exhibited AV septal defect .Complete AV canal defect in 10 hearts (45%) and partial AV canal defects in 4 hearts (18%).

In this study ventriculoarterial concordance was present in 63%. DORV in 10 (21.7%) and single ventricle in 7 (15.2%).In the Zuberbuhler series [53], ventriculoarterial connection was concordant in 64%, discordant 4% ,DORV in 18% of these cases. Aortic outflow obstruction was observed in only one patient (2.2%) in this study. High incidence of aortic outflow obstruction has been reported by Zuberbuhler et al[53] (45%) and Robert H Anderson [70] (27%).

In our study pulmonary atresia was observed in 4(8.7%) and pulmonary stenosis was seen in 7 (15.2%) patients comparable to the results observed by Robert H Anderson [70].

In this study, left axis deviation of P wave was seen in 34 patients (73.9%) with a normal PR interval in majority 26 (56.5%) patients.

Robert M Freedom and R Curtis Ellison[53] reported a leftward and superior P wave axis, the so called coronary sinus rhythm in 9 of 12 patients (75%) with the typical polysplenia syndrome. Developmental anomalies of the sinus venosus were present in all of these patients. All showed absence of renal to hepatic portion of the IVC with either and azygous or and hemiazygous extension. All patients had a leftward and superiorly oriented p wave axis (-50 to -80 degrees) .The PR interval was normal. In all patients, serial ECG records showed a transition from one atrial focus to another.

Several mechanisms have been postulated for coronary sinus rhythm:

1. Ongley [66] and his associates suggested that it could be attributed to the low position of the SA node near the coronary sinus.

2. Momma and Linde [11] have suggested that as polysplenia is a syndrome of bilateral left sidedness with suppression of normal right sided structures, the sinus node a right sided structure is poorly developed, Hence, the coronary sinus (derived from conduction tissues of the left sinus horn) becomes dominant resulting in coronary sinus rhythm.

This hypothesis is unlikely for 2 reasons as suggested by Robert M Freedom and R Curtis Ellison. [53]

1. Despite the absence of the coronary sinus in 2 of their patients, coronary sinus rhythm was still the dominant rhythm

2. In patients with incomplete development of left atrioventricular fold, the left side of the sinus venosus maintains continuity with the LA and is represented as termination of the LSVC in the LA ,absence of the coronary sinus ,and the characteristic coronary sinus ASD .There may be no sino atrial conduction tissue adjacent to the LSVC-LA junction. If this left sided conduction tissue becomes the dominant pacemaker the P wave vector should be directed from left to right and inferiorly suggesting atrial situs inversus, not leftward and superiorly as in coronary sinus rhythm.

Limitations of the study

As this study was done in a referral center for congenital heart diseases, it may not reflect the true percentage of venous anomalies in people without congenital heart defects

Usual echocardiography views do not delineate the systemic venous anomalies unless it is specifically searched for. Hence many venous anomalies might have been missed

The prevalence of ECG abnormities especially the shifting atrial focus may be evident only on serial ECG recordings which was not done for most of the patients included in this study.

Conduction system abnormalities, evaluated only by electrocardiogram may underestimate its true prevalence.

Conclusions

- Among patients with PLSVC, Isolated LSVC with absent right SVC was seen in 7 patients (7.7%) patients.
- The most common congenital heart diseases associated with PLSVC and Interrupted IVC were atrial septal defect and DORV respectively Cardiac malpositions like polysplenia and situs ambigus were common in interrupted IVC whereas it was rare in patients with PLSVC as the only venous anomaly .
- Majority of patients with interrupted IVC had left axis deviation of P wave whereas it was less common in the PLSVC group. Hence a leftward P axis is a reliable marker of interrupted IVC.
- Though transition from one atrial focus to another was common in Interrupted IVC, it did not produce any clinical manifestations.
- No patients with interrupted IVC needed pacemaker implantation whereas 6 patients with PLSVC underwent Pacemaker (for Sick sinus syndrome and complete heart block).
- Atrial arrhythmia was seen in 4 (4.4%) patients with PLSVC.
- In a critically ill infant who has coronary sinus rhythm, with congenital heart disease and heterotaxia, it might be expedient to approach cardiac catheterization from the upper extremity to avoid excessive time spent on cardiac catheterization.

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