

Clinico-Microbiological and Echocardiographic Assessment of Patients with Infective Endocarditis and New Onset Atrial Fibrillation.Pooja Batra¹, Priyadarshini Pal Singh²¹Emergency Medicine, Assistant Head Emergency Department, Indraprasth Apollo Hospital, Sarita Vihar, New Delhi, India²Director, Department of Accident and Emergency, Indraprasth Apollo Hospital, Sarita Vihar, New Delhi, India

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Conflict of interest: Nil

Abstract**Aim:** The purpose of this study was to investigate patient characteristics, microbiology, and echocardiographic findings of patients with infective endocarditis and new onset atrial fibrillation.**Methods:** This study was conducted at Indraprasth Apollo Hospital, Sarita Vihar, New Delhi. For purposes of analysis and comparison, we distinguished 3 groups according to the type of baseline heart rhythm during hospitalization and previous history of atrial: new onset atrial fibrillation group (n 50), patients with no previous history of atrial fibrillation and who were diagnosed as having new onset atrial fibrillation during hospitalization; sinus rhythm group (n 200), patients without a history of previous atrial fibrillation, who remained in sinus rhythm and who did not suffer atrial fibrillation during hospitalization; and previous atrial fibrillation group (n 50) included patients with previous atrial fibrillation (permanent, paroxysmal, or persistent).**Results:** Patients with new onset atrial fibrillation were older than those who remained in sinus rhythm. Concerning co-morbidities, chronic renal failure, and chronic obstructive pulmonary disease were more common in new onset atrial fibrillation group than in sinus rhythm group. At admission, heart failure and their radiological manifestations were more common in new onset atrial fibrillation group, whereas stroke and systemic embolism were equally present in all groups. Interestingly, blood levels of acute phase reactants at admission (C-reactive protein) were higher in patients with new onset atrial fibrillation. The microorganisms found in patients with NAF were not significantly different from those isolated in SR group and PAF group. Vegetations were equally present in groups. Vegetation size was similar in all groups. As regard to the presence of moderate- to-severe valvular insufficiency, no differences were found between patients with NAF and those who remained in SR.**Conclusion:** In conclusion, the occurrence of NAF in patients with IE was strongly associated with heart failure and higher in-hospital mortality independently from other relevant clinical variables.**Keywords:** New Onset Atrial Fibrillation, Infective Endocarditis, End Stage Kidney Disease.This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Infective endocarditis (IE) is an uncommon infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling cardiac device. [1,2] However, the mortality rate is estimated to be 10% at initial hospitalization and increases with long-term follow-up. [3–5] Therefore, identifying the patients at high risk of death is still urgent. Although relatively rare, IE continues to be characterized by increased morbidity and mortality and is now the third or fourth most common life-threatening infection syndrome, after sepsis, pneumonia, and intra-abdominal abscess. Globally, in 2010, IE was associated with 1.58 million disability-adjusted

life-years or years of healthy life lost as a result of death and nonfatal illness or impairment. [6]

Infective endocarditis (IE) in patients receiving HD has been reported for the first time in 1966. [8] It is now well known that IE in HD is significantly more common and causes greater morbidity and mortality than in the general population, being second only to cardiovascular disease as the leading cause of death in this group of patients. [7,9,10] Because of the peculiarity of this subset of patients, it has been recently proposed to add a fifth category (health-care-associated and HD-associated IE) in the actually four categories classification of IE (namely, native valve IE, prosthetic valve IE, IE in e.v. drug users, and nosocomial IE). [11,12]

Patients with ESRD have an increased incidence of degenerative heart valve disease, which is a major risk factor for IE.¹³ Calcific aortic stenosis¹³ mitral annular calcification with consequent mitral regurgitation, and/or stenosis¹³ and bioprosthetic valve degeneration¹⁴ are extremely frequent in this group of patients. Furthermore, degenerative heart valve disease is premature since it appears to begin 10–20 years earlier than in the general population.¹⁵ The accelerated development of valvular calcification in ESRD patients is thought to be related to the abnormalities of calcium–phosphorus homeostasis in the setting of secondary hyperparathyroidism and to the chronic micro-inflammatory milieu of uremia associated with ESRD. [13]

The purpose of this study was to investigate patient characteristics, microbiology, and echocardiographic findings of patients with infective endocarditis and new onset atrial fibrillation.

Materials and Methods

This study was conducted at Indraprasth Apollo Hospital, Sarita Vihar, New Delhi. To ensure consecutive enrollment, all patients who underwent echocardiography to rule out IE were clinically followed until a diagnosis was established. Only definite cases of left-sided IE were included. Right-sided episodes were excluded because of their different epidemiology, clinical characteristics, and prognosis.

This registry complies with the Declaration of Helsinki and was approved by the local ethical committee. All participants gave written informed consent. The proportion of missing data was <10% in all analyzed variables. For purposes of analysis and comparison, we distinguished 3 groups according to the type of baseline heart rhythm during hospitalization and previous history of atrial: new onset atrial fibrillation group (n 50), patients with no previous history of atrial fibrillation and who were diagnosed as having new onset atrial fibrillation during hospitalization; sinus rhythm group (n 200), patients without a history of previous atrial fibrillation, who remained in sinus rhythm and who did not suffer atrial fibrillation during hospitalization; and previous atrial fibrillation group (n 50) included patients with previous atrial fibrillation (permanent, paroxysmal, or persistent).

All patients underwent transthoracic and transesophageal echocardiography. A set of 3 blood cultures was obtained at admission and 3 additional blood cultures 48 to 72 hours later. If blood cultures were negative after 72 hours, specific serologic tests were done for Chlamydia, Brucella, Q fever, Legionella, Mycoplasma, and Bartonella.

Nosocomial and community-acquired IE were defined according to the study.¹⁶ Acute onset IE was applied when the time between the appearance of symptoms and hospital admission was <15 days. [17,18] Previous valvulopathy was defined as any kind of valvular heart disease and congenital valvular disease. Anemia was defined as a hemoglobin concentration below 9 g/dl; renal insufficiency was established when the serum creatinine concentration was >2 mg/ dl. Heart failure was diagnosed according to Framingham criteria. [19] Under the term of immunosuppression were included patients with human immunodeficiency virus and those who were on steroids or other immunosuppressive therapy. Persistent signs of infection and septic shock were defined as previously described. [16,20] The diagnosis of systemic embolism was based on clinical signs and data derived from imaging procedures according to the guidelines. [24]

The echocardiographic criteria used for definition and measurement of vegetations, abscesses, pseudoaneurysms, and fistulas have been described elsewhere. [21,22] Left atrial dimension was measured in M mode and 2-dimensional transthoracic echocardiography after the recommendations of the American Society of Echocardiography. [23]

Surgery was defined as early if done before antibiotic treatment was completed and was performed when any of the following occurred: refractory heart failure, recurrent embolism with persistent vegetations in the echocardiogram, persistent signs of infection, and fungal endocarditis. When a patient meeting surgical criteria did not undergo surgery, the reason was either because of patient rejection, unacceptably high surgical risk, or when the patient was too frail. Continuous variables are reported as a mean value and SD or median and interquartile range in cases of non-normality. Continuous variables were compared between the groups with a 2-tailed Student t test or Mann-Whitney U test when necessary. Categorical variables are expressed as a frequency and percentage and were compared with the chi-square test and Fisher's exact test when appropriate. In case of multiple categories, analysis of variance or Kruskal-Wallis test were used. Two multivariate logistic regression analyses were performed, one for prediction of mortality and another for detection of independent factors for heart failure. We included in the model the variables previously known to be associated to these events and those considered clinically relevant. When a variable statistically significant in the univariate analysis was not included in the multivariate analysis, the reason was collinearity or absence of change in the effect of AF. In addition, interactions between variables included in the model were

assessed in the model. The adjusted odds ratios (ORs) with 95% CIs for each variable have been calculated. All test were 2-tailed, and the differences were considered statistically significant

at p values <0.05. Statistical analysis was performed with PASW Statistics, version 17.0, (SPSS Inc. Chicago, Illinois).

Results

Table 1: Demographic and main clinical characteristics, electrocardiographic, radiological, and laboratory findings at admission in the patients with native left-sided infective endocarditis

	NAF (n=50)	SR (n=200)	PAF (n=50)	p
Age (years)	66.4 (10.2)	58.4 (14.4)	66.4 (12.2)	<0.001
Male	34 (68%)	136 (68%)	30 (60%) ^z	0.286
Community-acquired IE	32 (64%)	156 (78%)	29 (58%)	0.001
Previous valvulopathy	26 (52%)	88 (44%)	40 (80%)	<0.001
Anemia	12 (24%)	40 (20%)	16 (32%)	0.138
Chronic renal failure	10 (20%)	20 (10%)	8 (16%)	0.042
Diabetes	15 (30%)	34 (17%)	14 (28%)	0.054
Alcoholism	6 (12%)	20 (10%)	4 (8%)	0.908
Chronic obstructive pulmonary disease	7 (14%)	10 (5%)	8 (16%)	0.005
Malignant neoplasia	6 (12%)	22 (11%)	7 (14%)	0.712
Immunosuppression	4 (8%)	16 (8%)	6 (12%)	0.780
Symptoms to admission (days)	12.5 (7-57)	20.5 (7-60)	20 (7-35)	0.497
Acute onset (<15days)	25 (50%)	76 (38%)	22 (44%)	0.236
Fever at admittance	32 (63%)	281 (75.5%)	53 (72%)	0.138
Heart failure	26 (52%)	68 (34%)	26 (52%)	0.004
Acute renal failure	16 (32%)	40 (20%)	9 (18%)	0.134
Septic shock	6 (12%)	8 (4%)	4 (8%)	0.105
Chest pain	5 (10%)	22 (11%)	4 (8%)	0.950
Abdominal pain	5 (10%)	22 (11%)	4 (8%)	0.634
Splenomegaly	4 (8%)	20 (10%)	3 (6%) ^z	0.060
Confusional syndrome	10 (20%)	28 (14%)	8 (16%)	0.372
Coma	2 (4%)	4 (2%)	2 (4%)	0.910
Stroke				0.416
Hemorrhagic	1 (2%)	2 (4%)	2 (4%)	
Ischemic	7 (14%)	24 (12%)	2 (4%)	
Systemic embolism	9 (18%)	44 (22%)	8 (16%)	0.260
Hematuria	4 (8%)	8 (4%)	2 (1%)	0.186
Arthritis/Spondylodiscitis	5 (10%)	34 (17%)	4 (8%)	0.050
Anticoagulation	12 (24%)	12 (6%)	35 (70%)	<0.001
Second and third degree AV block	2 (4%)	4 (2%)	2 (1%)	0.650
Left bundle-branch block	3 (6%)	4 (2%)	5 (10%)	0.012
Cardiomegaly	36 (72%)	84 (42%)	30 (70%)	<0.001
Pleural effusion	22 (44%)	44 (22%)	13 (26%)	0.005
C-reactive protein (mg/dl) ^x	17.9 (6.9-115.3)	14.3 (4.8-67.8)	6.9 (2.9-14.8)	0.024 ^z
Hemoglobin (g/dl)	11 (2.2)	11.1 (2.1)	11 (2)	0.920
Platelets	228x10 ³ (124x10 ³)	215x10 ³ (141x10 ³)	196x10 ³ (99x10 ³) ^z	0.118

Patients with new onset atrial fibrillation were older than those who remained in sinus rhythm. Concerning co-morbidities, chronic renal failure, and chronic obstructive pulmonary disease were more common in new onset atrial fibrillation group than in sinus rhythm group. At admission, heart failure and their radiological manifestations were

more common in new onset atrial fibrillation group, whereas stroke and systemic embolism were equally present in all groups. Interestingly, blood levels of acute phase reactants at admission (C-reactive protein) were higher in patients with new onset atrial fibrillation.

Table 2: Microbiological profile

	NAF	SR	PAF	p
<i>Streptococcus bovis</i>	2 (4%)	12 (6%)	2 (4%)	0.670
Other <i>estreptococci</i>	5 (10%)	18 (9%)	4 (8%)	0.855
<i>Enterococci</i>	6 (12%)	16 (8%)	5 (10%)	0.732
<i>Staphylococcus aureus</i>	7 (14%)	34 (17%)	8 (16%)	0.766
Coagulase negative <i>staphylococci</i>	10 (20%)	22 (11%)	9 (18%)	0.208
Gram negative <i>bacilli</i>	1 (2%)	4 (2%)	2 (4%)	0.924
Fungi	0 (0%)	2 (1%)	2 (4%)	0.350
HACEK Group	0 (0%)	2 (1%)	0 (0%)	0.510
Anaerobes	0 (0%)	1 (0.5%)	1 (1%)	0.712
Polymicrobial	3 (6%)	10 (5%)	4 (8%)	0.403
Others	2 (4%)	6 (3%)	2 (4%)	0.740
Negative cultures	12 (24%)	28 (14%)	8 (16%)	0.260

The microorganisms found in patients with NAF were not significantly different from those isolated in SR group and PAF group.

Table 3: Echocardiographic findings

	NAF	SR	PAF	p
Location of the infection				
Aortic native valve	28 (56%)	112 (56%)	26 (52%)	0.710
Mitral native valve	30 (60%)	120 (60%)	30 (60%)	0.965
Left atrial dimension (mm)	16 (8)	12 (6)	26 (13)	<0.001 ^z
Vegetations				
Detection by echocardiography	49 (98%)	180 (90%)	42 (84%)	0.036
Vegetation size (mm)	12 (9.4-18.3)	12.7 (9-18.5)	12 (7-18.4)	0.808
Moderate-severe valvular regurgitation	40 (80%)	170 (85%)	36 (72%)	0.120 ^z
Periannular complications	15 (30%)	48 (24%)	10 (20%)	0.585
Abscess	8 (16%)	24 (12%)	9 (18%)	0.280
Pseudoaneurysm	9 (18%)	32 (16%)	4 (8%) ^z	0.170
Fistula	1 (2%)	4 (2%)	1 (1%)	0.855

Vegetations were equally present in groups. Vegetation size was similar in all groups. As regard to the presence of moderate- to-severe valvular insufficiency, no differences were found between patients with NAF and those who remained in SR.

Table 4: Clinical events during in-hospital

	NAF	SR	PAF	p
Heart failure	40 (80%)	116 (58%)	35 (70%)	0.007
CNS embolism	7 (14%)	24 (12%)	3 (6%)	0.320
Systemic embolism	15 (30%)	64 (32%)	12 (24%)	0.415
Acute renal insufficiency	26 (52%)	96 (48%)	30 (60%)	0.120
Septic shock	13 (26%)	32 (16%)	11 (22%)	0.125
Cardiac surgery	25 (50%)	116 (58%)	26 (52%)	0.502
Death	24 (48%)	50 (25%)	18 (36%)	0.003

Heart failure was significantly more frequent in patients with NAF.

Discussion

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults and has been independently related to increased morbidity and mortality. [25] It is also well known the association between new-onset AF (NAF) and mortality in patients hospitalized with severe sepsis [26,27] or heart failure. [28] Atrial fibrillation (AF) is a common arrhythmia in patients with acute conditions attributed to inflammation and hemodynamic change. [29] New-onset AF has a close association with poor outcomes in several conditions, including sepsis, heart failure (HF), and cardiac surgery.

[30,31] Ferrera and co-workers enrolled 507 patients with native left-sided IE, 10.3% of whom developed new AF. They demonstrated that new-onset AF was associated with HF and higher in-hospital mortality. [32]

Patients with new onset atrial fibrillation were older than those who remained in sinus rhythm. Concerning co-morbidities, chronic renal failure, and chronic obstructive pulmonary disease were more common in new onset atrial fibrillation group than in sinus rhythm group. At admission, heart failure and their radiological manifestations were more common in new onset atrial fibrillation group,

whereas stroke and systemic embolism were equally present in all groups. Interestingly, blood levels of acute phase reactants at admission (C-reactive protein) were higher in patients with new onset atrial fibrillation. The microorganisms found in patients with NAF were not significantly different from those isolated in SR group and PAF group. Regarding demographic and co-morbidity conditions, patients with NAF were older, left atrial dimension was larger, and they had more frequently chronic renal failure and chronic obstructive pulmonary disease. With aging, the extent of atrial fibrosis increases. [33] Fibrosis results from increased collagen deposit and is considered as an important factor in the development and maintenance of the arrhythmia. [34,35] Chronic renal failure is a common co-morbidity in patients with AF. [36] It is well known that chronic renal failure favors tissue fibrosis and hypertension and therefore the onset and establishment of AF.

Vegetations were equally present in groups. Vegetation size was similar in all groups. As regard to the presence of moderate- to-severe valvular insufficiency, no differences were found between patients with NAF and those who remained in SR. Although AF is associated with increased risks of major cardiovascular events such as stroke, heart failure, and death,¹⁷ the event rates of these competing outcomes in IE have not been analyzed. In the herein series, the rate of stroke and systemic embolism was not higher in episodes with NAF.³⁷ Heart failure was significantly more frequent in patients with NAF. Acute AF may lead to overt heart failure, the symptoms of which often improve after AF termination.¹⁶ In IE, heart failure may be secondary to rapid AF and severe valvular insufficiency among other factors. Understanding the mechanism for developing heart failure in patients with IE is an important goal. In our series, NAF was found to be strongly associated to heart failure. Loss of atrioventricular synchrony, rapid irregular ventricular response, and lack of atrial contraction reduce diastolic filling and cardiac output. In this scenario, atrial and pulmonary capillary pressures increase perpetuating heart failure and AF. In IE, severe valvular insufficiency secondary to valvular destruction by the infection may also contribute to heart failure. Interestingly, moderate-to-severe valvular insufficiency was not more common in episodes with NAF.

As heart failure is the most frequent complication of IE and represents the most common indication for surgery,³⁸ it is particularly relevant to stand out that in our series, the proportion of patients who developed heart failure was greater in episodes with AF (NAF and previous); however, these 2 groups had a lower rate of moderate-to-severe valvular insufficiency. These facts suggest that

heart failure in some patients with left-sided IE and AF could be solved by heart rate or rhythm control instead of with valvular surgery. In our series, surgery was performed more frequently in patients with heart failure and SR than in those with heart failure and AF.

Conclusion

In conclusion, the occurrence of NAF in patients with IE was strongly associated with heart failure and higher in-hospital mortality independently from other relevant clinical variables.

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