Diastolic function abnormalities in rheumatoid arthritis: relation with duration of disease

Udayakumar N, Venkatesan S, Rajendiran C

ABSTRACT

Introduction: There are limited studies on the prevalence of diastolic dysfunction in rheumatoid arthritis (RA) from the Indian subcontinent. The aim of this study was to evaluate left ventricular filling abnormalities in patients with RA without clinically-evident cardiovascular manifestations, and to correlate it with disease duration.

Methods: 45 patients affected with RA according to the American Rheumatism Association criteria, were selected without evidence of cardiac disease, and compared with age- and sex-matched control subjects. All patients and the control group were submitted to M-mode, two-dimensional and Doppler echocardiography. The following diastolic parameters were evaluated: peak of early diastolic (E) and late diastolic (A) mitral flow velocity, E/A ratio, isovolumic relaxation time (IVRT), ejection fraction and fractional shortening.

Results: In RA patients, left ventricular filling abnormalities were found characterised by a reduced E/A ratio (mean [SD] 0.98 [0.22] versus controls 1.09 [0.11]; p-value equals 0.004), prolonged IVRT (75.77 [8.12] ms versus 70.43 [2.94] ms; p-value equals 0.001) and increased late diastole flow velocity (76.91 [11.61] cm/s versus 70.11 [5.32] cm/s; p-value equals 0.001). In the group of patients, a negative correlation was found between E/A ratio and disease duration (Pearson correlation, r equals –0.56, p-value equals 0.001), indicating diastolic dysfunction with increasing disease duration. A strong correlation was also found between IVRT and disease duration (r equals 0.66, p-value equals 0.01) and also between late diastolic flow velocity and disease duration (r equals 0.61, p-value equals 0.001).

Conclusion: The present study confirms a high frequency of left ventricular diastolic dysfunction characterised by impaired E/A ratio, prolonged IVRT and increased late diastole flow velocity in patients with RA without evident cardiovascular disease. The correlation between transmitral flow alteration and disease duration suggests a subclinical myocardial involvement with disease progression. This may be relevant to the high incidence of cardiovascular deaths observed in patients with RA.

Keywords: cardiovascular disease, congestive heart failure, diastolic dysfunction, rheumatoid arthritis

Singapore Med J 2007; 48(6):537–542

Department of Internal Medicine, Madras Medical College, Chennai 600003, India

Udayakumar N, MD
Resident

Rajendiran C, MD
Associate Professor

Department of Cardiology

Venkatesan S, MD, DM
Assistant Professor

Correspondence to:
Dr N Udayakumar
Tel: (91) 45 2238 2332
Fax: (91) 44 2432 4293
Email: udhaykumar81@yahoo.co.in

INTRODUCTION

Long-term survival of patients with rheumatoid arthritis (RA) is shorter than that of the general population or control subjects without RA.[1] Among the different causes of death, increased mortality from heart disease with high prevalence of congestive cardiac failure has been reported in many studies.[1,2] del Rincon et al observed that the higher incidence of cardiovascular complications in these patients was independent of the influence of traditional cardiovascular risk factors.[3] However, cardiac disease is often clinically silent and is rarely a severe life-threatening complication in RA. Cardiac failure is the result of either systolic or diastolic dysfunction or both. Left ventricular diastolic dysfunction is usually attributable to common structural abnormalities, such as hypertrophy or interstitial fibrosis, and impaired myocyte relaxation resulting from ischaemia.

Because primary diastolic dysfunction is an important cause of heart failure, as it often is a silent alteration preceding systolic dysfunction,[4] knowledge of this complication in patients with RA without clinically-evident cardiac disease may be important to improve patient survival. A number of recent studies have reported the presence of diastolic dysfunction in patients with RA without clinically-evident cardiac disease.[5,6] Studies from

India have traditionally highlighted the low prevalence of mild extra-articular manifestations seen in our group of patients. The frequency and distribution of the IL-1 receptor antagonist gene polymorphisms in India are also substantially different from other populations and ethnic groups.[7] This may explain the different presentation of disease in India. However, a recent study from India highlighted that one-third of patients with RA who are asymptomatic have subclinical atherosclerosis.[8] But there have been limited studies on subclinical cardiac dysfunction in our group of patients with RA. With this background, we designed a study to identify the prevalence of diastolic dysfunction in RA patients and correlated them with the disease duration.

METHODS

The study was carried out on 45 consecutive patients (nine men and 36 women, mean (standard deviation [SD]) age 34.8 (6.7) years, range 21–50 years) attending the rheumatology outpatient department of Madras Medical College and General Hospital, with an established diagnosis of RA, as defined by the American Rheumatism Association 1987 criteria. Duration of the disease ranged from one to 17 years. Informed consent was obtained from subjects enrolled and the study was approved by the hospital ethics committee. 45 normal subjects referred for echocardiogram without a clinical diagnosis of connective tissue disorders, such as systemic sclerosis or RA, and without evidence of cardiorespiratory diseases, (nine men and 36 women, mean (SD) age 35.4 (6.5) years, range 23–52 years) were selected as controls.

None of the subjects included in the study had evidence of cardiac disease, hypertension and diabetes mellitus, as assessed by history, physical examination, chest radiography and standard 12-lead ECG. In view of the radiation exposure involved in the study, patients were excluded if they were pregnant or planning a pregnancy. All had been treated with nonsteroidal anti-inflammatory drugs (NSAID) (diclofenac, 100–150 mg/day) daily. All of them have been treated and were in treatment with one or more disease-modifying antirheumatic drug (DMARD), including chloroquine, sulphasalazine, and methotrexate. Treatment with a DMARD was initiated when RA was diagnosed.

Patients were considered seropositive if the rheumatoid factor (by nephelometry) was positive on at least two separate occasions during the course of the disease. A questionnaire that was prepared noted the duration of RA, extra-articular complications, the use of current and previous disease-modifying drugs, corticosteroid use, and early morning joint stiffness. A detailed clinical examination was performed. All patients had venous blood taken for full blood count, renal and liver functions and C-reactive protein. Immunological investigations included rheumatoid factor (latex agglutination test) and antinuclear antibodies. All patients underwent echocardiography, electrocardiography (ECG) and chest radiography.

Two-dimensional and M-mode echocardiography (Hewlett-Packard, Andover, MA, USA) were performed with the patient in the left lateral position. One senior cardiologist performed all the echocardiography. The following variables were assessed: aortic root diameter, left atrial diameter, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, thickness of the interventricular septum, thickness of the left ventricular posterior wall and right ventricular end-diastolic diameter. Fractional shortening and ejection fraction were calculated according to Simpson's formula. Doppler echocardiography was used to obtain transmitral flow from the apical four-chamber view. To record transmitral flow, the sample volume was positioned at the tip of the

Table I. Echocardiographical and Doppler variables in patients and control subjects.

	Patients (n = 45)	Controls (n = 45)	p-value
Left atrium diameter (mm)	27.60 ± 4.47	24.96 ± 2.45	0.01*
Aorta diameter (mm)	29.91 ± 1.50	30.18 ± 1.15	0.35
Left ventricular end-diastolic dimension (mm)	50.04 ± 3.78	45.99 ± 3.42	0.001*
Left ventricular end-systolic dimension (mm)	30.48 ± 2.47	29.04 ± 2.29	0.005*
Ejection fraction (%)	70.72 ± 2.26	70.58 ± 1.94	0.75
Fractional shortening (%)	38.32 ± 3.29	39.07 ± 3.37	0.22
Early diastolic flow velocity, E (cm/s)	73.32 ± 9.04	76.32 ± 5.59	0.06
Late diastolic flow velocity, A (cm/s)	76.92 ± 11.62	70.11 ± 5.33	0.001*
Isovolumic relaxation time (ms)	75.77 ± 8.13	70.43 ± 2.94	0.001*
E/A ratio	0.98 ± 0.23	1.09 ± 0.11	0.004*
Pulmonary artery pressure (mmHg)	27.49 ± 12.66	20.40 ± 8.88	0.003*

* $p < 0.05$ is significant

leaflets of mitral valve. The following variables were examined as parameter of the left ventricular filling: peak of early diastolic (E) and late (or atrial) diastolic (A) flow velocity, E/A ratio, and isovolumic relaxation time (IVRT). When taken alone, normally the E/A ratio is greater than one; in late relaxation, it decreases to below one, and this is an indicator of diastolic dysfunction.[9,10] We have taken an E/A ratio of less than one as suggestive of diastolic dysfunction.

Continuous data were described as mean and SD, and categorical variables as numbers. Comparisons between two categories were made using Student t-test (two-tailed) for continuous variables. To analyse categorical data, we performed the chi-square test. Pearson correlation was used to correlate continuous variables, such as disease duration and parameters of diastolic dysfunction.

RESULTS

Women outnumbered men in the study population, with 36 women and nine men. The mean age at the time of diagnosis was 34.8 ± 6.7 years. The mean disease duration in patients was 5.1 years. During the course of the disease, extra-articular manifestations were observed in almost 58% (n = 26) of the patients. Rheumatoid nodules were found in ten patients, all of whom were rheumatoid factor positive. The main echocardiographical and Doppler findings in this series of patients with RA without clinical evidence of cardiovascular disease are summarised in Table 1. The mean values of diameters in the left cavities were within the normal ranges. It was also the case for the mean left ventricular ejection fraction (Table I). 19 (42.2%) of the patients exhibited left ventricular diastolic dysfunction (E/A < 1) due to impaired relaxation.

There was a significant difference between the two groups and without RA regarding the ventricular cardiac chamber dimensions, both end-systolic and end-diastolic compared to the controls ($p < 0.05$). But there was no difference between the ejection fraction and fractional shortening of the left ventricle. In RA patients, we found abnormalities of the left ventricular filling characterised by increased late diastolic mitral filling velocity, A (76.92 ± 11.62 cm/s versus 70.11 ± 5.33 cm/s, $p = 0.001$), prolonged IVRT (75.77 ± 8.13 ms versus 70.43 ± 2.94 ms, $p = 0.001$) and by a reduced E/A ratio (0.98 ± 0.23 versus 1.09 ± 0.11, $p = 0.004$) compared to the controls (Table I).

We could not do further subgroup analyses in patients with RA who were treated with NSAID alone or with DMARD alone, as all the patients in our study were on a combination therapy of both groups of drugs; patients were started on DMARD early in their disease to prevent long-term disabilities. In this group of patients, we found a positive correlation between IVRT and disease duration ($r = 0.67$, $p = 0.001$), and late diastolic mitral filling velocity, A and disease duration ($r = 0.61$, $p = 0.001$), and a negative

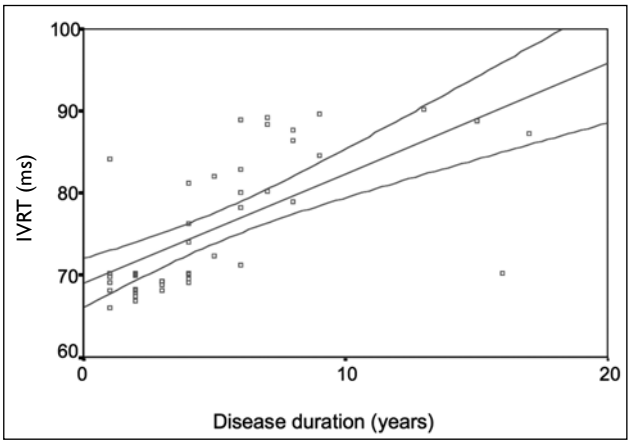

Fig. 1 Graph shows a positive correlation between IVRT and disease duration.
Correlation coefficient, r = 0.67
Slope, p = 0.001

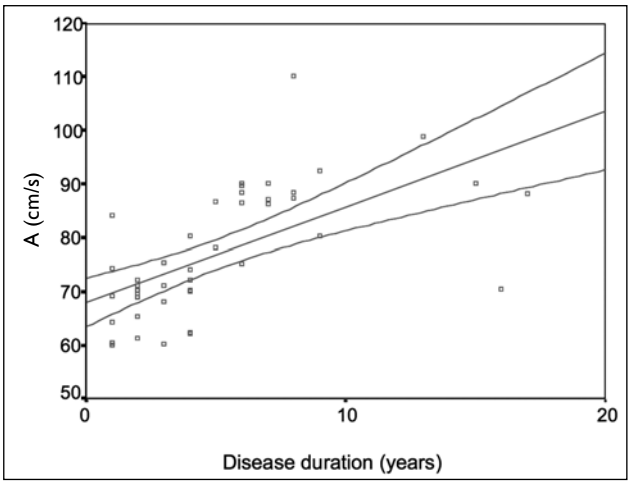

Fig. 2 Graph shows a positive correlation between late diastolic mitral filling velocity (A) and disease duration.
Correlation coefficient, r = 0.61
Slope, p = 0.001

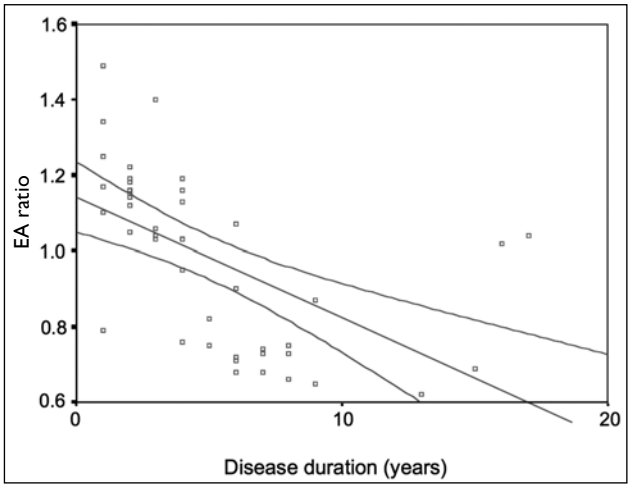

Fig. 3 Graph shows a negative correlation between diastolic dysfunction and disease duration.
Correlation coefficient, r = -0.19
Slope, p = 0.21 (not significant)

Table II. Echocardiographic and Doppler variables in patients with and without diastolic dysfunction.

	Patients (n = 19) [E/A < 1]	Patients (n = 26) [E/A > 1]	p-value
Left atrium diameter (mm)	27.26 ± 6.49	27.85 ± 2.17	0.67
Aorta diameter (mm)	30.11 ± 1.91	29.77 ± 1.10	0.46
Left ventricular end-diastolic dimension (mm)	53.17 ± 2.33	47.75 ± 2.88	0.001*
Left ventricular end-systolic dimension (mm)	32.80 ±1.50	28.78 ± 1.42	0.001*
Ejection fraction (%)	70.71 ± 1.73	70.73 ± 2.61	0.97
Fractional shortening (%)	35.22 ± 2.53	40.59 ± 1.35	0.001*
Early diastolic flow velocity, E (cm/s)	65.18 ± 4.94	79.27 ± 6.24	0.001*
Late diastolic flow velocity, A (cm/s)	87.85 ± 7.73	68.92 ± 6.10	0.001*
Isovolumic relaxation time (ms)	83.57 ± 5.34	70.07 ± 3.94	0.001*
E/A ratio	0.75 ± 0.09	1.15 ± 0.11	0.001*
Pulmonary artery pressure (mmHg)	32.47 ± 12.09	23.85 ± 12.00	0.02*

* $p < 0.05$ is significant

correlation between the E/A ratio and disease duration ($r = -0.19$, $p = 0.21$) (Figs. 1–3).

19 patients (42.2%) in the RA group had an E/A ratio of less than one, and this was taken as an indicator of diastolic dysfunction. Among the control population, only two patients (4.4%) had evidence of diastolic dysfunction. The RA patients with evidence of diastolic dysfunction were then compared with RA patients with an E/A ratio of more than one, and the results are summarised in Table II. To further investigate the implication of the left ventricular diastolic dysfunction in patients with RA without clinically-evident cardiovascular disease, we assessed whether patients with RA who had left ventricular diastolic dysfunction had some clinical or investigatory peculiarities that might help identify these patients. Rheumatoid factor was significantly positive in patients with RA with left ventricular diastolic dysfunction (89.5% versus 42.3%; $p = 0.02$). However, no statistically significant differences in gender, presence of extra-articular manifestations, and cumulative prednisone doses were found (data not shown).

DISCUSSION

In unselected patients with RA, a wide spectrum of echocardiographical and Doppler abnormalities has been observed.[11] An important step forward in our understanding of cardiovascular disease in RA cases may be to confirm whether cardiac abnormalities were also present in actively-treated patients with RA, where underlying cardiac disease or concomitant cardiovascular risk factors that might be implicated in the development of cardiac abnormalities have been excluded. In our study of South Indian patients with RA but without cardiovascular risk factors or clinically-evident cardiac disease, a number of echocardiographical abnormalities were observed. Left ventricular diastolic dysfunction was observed in 19 out of 45 patients (42.2%). Moreover, the mean age of patients without any cardiorespiratory disease was only 34.8 ± 6.7 years; and this young age cannot explain the diastolic dysfunction.

However, there are several potential limitations to the study: the study population was small; none of the control patients were on DMARD, which makes the comparison between the study and control population difficult; and there have not been any previous reports of induced diastolic dysfunction due to use of DMARD. Thus, the statistically significant difference cannot be explained. In addition, doing a subgroup analysis on this small population would not be accurate. However, although the study group is relatively small, a significant number of patients (19) had evidence of diastolic dysfunction, and one of the aims of this study is to highlight this observation to the medical community.

14 years ago, Finnish investigators showed abnormalities in the left ventricular diastolic function in 12 young men with RA without clinically-evident cardiac disease, compared with 14 healthy controls.[12] Later, Italian investigators described the presence of diastolic abnormalities in both men and women with RA.[13] Diastolic dysfunction was observed despite normal left ventricular systolic function, compared with matched controls. Abnormal relaxation time was mainly responsible for the impairment in the left ventricular filling.[13] More recently, a number of studies from Europe have reported the presence of diastolic dysfunction in patients with RA without clinically-evident cardiac disease.[5,6] Similar abnormalities have been observed in patients with ankylosing spondylitis and psoriatic arthritis.[14,15]

Because primary diastolic dysfunction is an important cause of heart failure, as it often is a silent alteration preceding systolic dysfunction,[4] knowledge of this complication in patients with RA without clinically-

evident cardiac disease may be important to improve patient survival. Similar to our study, a correlation between diastolic dysfunction and disease duration in active patients with RA has also been reported in studies from Europe.[6,16] In a study of juvenile RA patients from India, the presence of both systolic and diastolic dysfunctions was observed in 35 patients with a correlation to disease duration.[17] Our results too indicate that patients with RA have a different mitral flow velocity pattern compared to controls. In the patients, we found an increased mitral flow velocity pattern at atrial contraction and a decreased E/A ratio. As the subjects were selected to clinically exclude loading alterations and other factors that can affect diastolic filling, there is no reason to think that the two groups were not homogeneous and comparable.

Our results confirm the presence of diastolic abnormalities in RA patients from India. The other concern is that all these patients were being treated with DMARDs. What is the clinical outcome of such abnormalities? Diastolic dysfunction has been recognised as a primary cause of congestive cardiac failure. In RA patients, an increased prevalence of congestive cardiac failure is well-documented.[1,2] Such an increased morbidity does not seem to be related to hypertension or ischaemic heart disease. It could be due to a more extensive involvement of the heart with consequent changes in the left ventricular structure that might manifest themselves in abnormalities of the left ventricular diastolic function, subsequently leading to systolic dysfunction. As no specific tissue typing studies were performed in our patients, we could only guess that these diastolic abnormalities could be caused by left ventricular structural alterations (i.e. an increase or modification of interstitial connective tissue within the myocardium).

In our study, we found a statistically significant correlation between disease duration and alteration of diastolic function expressed as late diastolic mitral filling velocity, A and IVRT. The correlation between transmitral flow alteration and disease duration suggests a subclinical myocardial involvement with disease progression. This observation could be of a therapeutic benefit in sensitising physicians to the benefits of controlling the disease progression and periodic screening by echocardiography of RA patients. This study raises an important issue – we have found a high prevalence of diastolic filling abnormalities in RA patients, observed in 42.2% of asymptomatic RA patients who were being treated with DMARDs. Recent studies have highlighted the increasing prevalence of diastolic heart failure and the prognosis being equally bleak, similar to patients with reduced ejection fraction (systolic heart failure).[18,19]

This study highlights that patients from India are equally susceptible to complications similar to other populations. Therefore, routine screening of RA patients with Doppler echocardiography may detect subclinical cardiac involvement and corrective measures could be instituted before clinically-evident cardiac failure ensues. Cardiovascular manifestations are common in RA patients. The relation between transmitral flow alteration and disease duration suggests a subclinical myocardial involvement with disease progression, and may be related to the high incidence of cardiovascular deaths in patients with RA. We recommend screening echocardiography for all patients with RA.

REFERENCES

1. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously – predictive markers, socioeconomic status and comorbidity. J Rheumatol 1986; 13:841-5. Comment in: J Rheumatol 2005; 32:17-9.
2. Mutru O, Laakso M, Isomaki H, Koota K. Cardiovascular mortality in patients with rheumatoid arthritis. Cardiology 1989; 76:71-7.
3. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001; 44:2737-45.
4. Little WC, Cheng CP. Diastolic dysfunction. Cardiol Rev 1998; 6:231-9.
5. Di Franco M, Paradiso M, Mammarella A, et al. Diastolic function abnormalities in rheumatoid arthritis. Evaluation by echo Doppler transmitral flow and pulmonary venous flow: relation with duration of disease. Ann Rheum Dis 2000; 59:227-9.
6. Arslan S, Bozkurt E, Sari RA, Erol MK. Diastolic function abnormalities in active rheumatoid arthritis evaluation by conventional Doppler and tissue Doppler: relation with duration of disease. Clin Rheumatol 2006; 25:294-9.
7. Grover S, Tandon S, Misra R, Aggarwal A. Interleukin-1 receptor antagonist gene polymorphism in patients with rheumatoid arthritis in India. Indian J Med Res 2006; 123:815-20.
8. Grover S, Sinha RP, Singh U, et al. Subclinical atherosclerosis in rheumatoid arthritis in India. J Rheumatol 2006; 33:244-7. Comment in: J Rheumatol 2006; 33:201-3.
9. Montero A, Gentile F, Gunaltieratti C, et al. Left ventricular diastolic parameters in 288 normal subjects from 20 to 80 years old. Eur Heart J 1995; 16, 94-105.
10. Thomas JD, Newel JB, Choong CYP, Weyman AE. Physical and physiological determinants of transmitral velocity: numerical analysis. Am J Physiol 1991; 260(5 Pt 2):H1718-31.
11. Dawson JK, Goodson NG, Graham DR, Lynch MP. Raised pulmonary artery pressures measured with Doppler echo-cardiography in rheumatoid arthritis patients. Rheumatology 2000; 39:1320-5.
12. Mustonen J, Laakso M, Hirvonen T, et al. Abnormalities in left ventricular diastolic function in male patients with rheumatoid arthritis without clinically evident cardiovascular disease. Eur J Clin Invest 1993; 23:246-53.
13. Corrao S, Salli L, Arnone S, et al. Echo-Doppler left ventricular filling abnormalities in patients with rheumatoid arthritis without clinically evident cardiovascular disease. Eur J Clin Invest 1996; 26:293-7
14. Brewerton DA, Gibson DG, Goddard DH, et al. The myocardium in ankylosing spondylitis. A clinical, echocardiographic, and histo-pathological study. Lancet 1987; 1:995-8.
15. Rowe IF, Gibson DG, Keat AC, Brewerton DA. Echocardiographic diastolic abnormalities of the left ventricle in inflammatory joint disease. Ann Rheum Dis 1991; 50:227-30.
16. Montecucco C, Gobbi G, Perlini S, et al. Impaired diastolic function in active rheumatoid arthritis. Relationship with disease duration. Clin Exp Rheumatol 1999; 17:407-12.
17. Bharti BB, Kumar S, Kapoor A, et al. Assessment of left ventricular systolic and diastolic function in juvenile rheumatoid arthritis. J Postgrad Med. 2004; 50:262-5.
18. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J

Med. 2006; 355:251-9. Comment in: N Engl J Med 2006; 355:308-10. N Engl J Med 2006; 355:1828; author reply 1830-1. N Engl J Med 2006; 355:1829-30; author reply 1830-1. N Engl J Med 2006; 355:1829; author reply 1830-1.

19. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006; 355:260-9. Comment in: ACP J Club 2006; 145:78. Evid Based Med 2006; 11:185. N Engl J Med 2006; 355:308-10. N Engl J Med 2006; 355:1828-9; author reply 1830-1. N Engl J Med 2006; 355:1828; author reply 1830-1. N Engl J Med. 2006 Oct 26;355(17):1829-30; author reply 1830-1. N Engl J Med. 2006 Oct 26;355(17):1829; author reply 1830-1.

Singapore Medical Journal Honour Roll of Editors

Honorary Editor	Term of Service
Gwee Ah Leng	1960 – 1971
Tan Kheng Khoo	1971 – 1975
Lim Pin	1975 – 1978
Feng Pao Hsi	1978 – 1987
Chee Yam Cheng	1988 – 1995
Tan Choon Kim	1995 – 1996
Kua Ee Heok	1996 – 1999
C Rajasoorya	2000 – 2003
Wilfred CG Peh	2004 – Present