Thrombo-embolism in Patients with Myocarditis

M SADIQ A W RATHORE* M YOUNIS *N HAIDER F MASUD ASIF-UR-REHMAN*
Department of Paediatric Cardiology, The Children's Hospital and The Institute of Child Health, Lahore.
**Associate Professor of Paediatrics The Children's Hospital and The institute of Child Health, Lahore*
Correspondence to Prof. Masood Sadiq, Paediatric Cardiology E-mail: drmasoodsadiq@hotmail.com

Background: Myocarditis and dilated Cardiomyopathy continues to be an important cause of hospital admission in our part of the world. Systemic embolism due to thrombi in left ventricle is a rare but important complication of these patients.
Study objectives: To determine the incidence, course and outcome of thrombo-embolism in children with dilated dysfunctioning heart due to acute myocarditis or dilated Cardiomyopathy. **Design:** A 5 year analysis (December 1999- Nov 04) of all children under 16 years of age admitted and diagnosed as having myocarditis or dilated Cardiomyopathy in a single tertiary care center. **Patients and Methods:** The charts and echocardiography records of all patients with dilated dysfunctioning heart and systemic thrombo-embolism were reviewed. Data was reviewed for mode of presentation, age, hospital course and outcome. Echocardiography data was reviewed with special reference to the size, function and presence of thrombus in LV. **Results:** Of all admissions to the paediatric cardiology unit over the study period, myocarditis and dilated Cardiomyopathy was the underlying lesion in 405 patients. The mean age of patients was 2.1 $\pm$ 4 years. Systemic embolism was the presenting feature in 28 (6.9%) patients (Group A); while another 17 (4.2%) developed it during the hospital stay (Group B). Another 5 patients had thrombus in the LV but did not develop embolism. All 50 patients showed seriously impaired LV function with mean ejection fraction (EF) for those with vs. those without thrombo-embolism was 17.5 $\pm$ 5.5 vs. 20.0 $\pm$ 6.9 ($p = 0.08$). The groups were similar with respect to other baseline characteristics, co morbid illnesses, and drug therapies other than anticoagulants. In group A 26/28 patients presented with a stroke. Only 6 had a thrombus in LV at the time of admission. All 28 patients with or without LV thrombus were treated with heparin and then oral anticoagulant warfarin. There were two deaths. In group B, 3/17 patients had thrombus in the LV on echocardiography at presentation. They were started anticoagulation but still went on to develop a stroke. There were 2 deaths in this group as well. **Conclusions:** Myocarditis and dilated Cardiomyopathy is an important cause of hospital admission in our set up accounting for 15% of all admissions to a paediatric cardiology unit. These patients are at risk of developing thrombo-embolism, which may well be the presenting feature. The risk is higher in patients with lower ejection fraction of the LV. All patients with EF below 17% should be treated with prophylactic anticoagulation. A peripheral embolic event adds to morbidity and is related to poor long-term survival in this patient group.
Key Words: congestive heart failure, left ventricular thrombus, systemic embolism

Myocarditis and dilated Cardiomyopathy are an important acquired heart disease in this part of the world[1]. Infectious myocarditis is a common condition, which often passes unrecognized, and the true incidence is thus unknown. Lymphocytic myocarditis has been recorded in 1.06% of 12,747 unselected routine autopsies performed over a 10-year period in Sweden[3]. Dilated Cardiomyopathy (DCM) had an estimated frequency of 7.5-10% per 100,000 inhabitants per year in the same study. In a reported study from the our own institution[28], this disease followed a seasonal pattern, that is, a much larger number of acute cases were seen in months of early spring (February, March) and winter (October, November) than the rest of year. The true incidence of viral myocarditis in children is unknown. Although a 10-year population-based study in Australia reported an incidence of 11 cases of all types of Cardiomyopathy per million children less than 20 years old[1], many children who have mild disease probably never present to medical attention.

Every pediatrician must maintain a high index of suspicion for myocarditis in any patient who presents with tachycardia and signs of respiratory distress, especially in the setting of poor clinical cardiac output. Prompt recognition of patients who have potential myocarditis is necessary to prevent life-threatening deterioration.

Systemic embolism due to thrombi in left ventricle is a rare but important complication of these patients and may well be the first presentation of a child with myocarditis or dilated Cardiomyopathy. There is however, very limited information in the medical literature that addresses the risks of thrombo-embolism among patients with severe left ventricular (LV) dysfunction[3-14]. The need to develop preventive and therapeutic evidence-based approaches for these patients is apparent.

In this study, we sought to do the following: (1) identify the incidence of thrombo-embolism and prevalence of LV thrombus by two-dimensional echocardiography among patients with myocarditis and or dilated Cardiomyopathy, (2) describe the characteristics of patients with LV thrombus, and (3) determine the course and outcome of thrombo-embolism in children with acute myocarditis and dilated Cardiomyopathy.

Materials and Methods

We reviewed the records of 50 consecutive patients with dilated dysfunctioning LV and a provisional diagnosis of myocarditis and or dilated Cardiomyopathy who had

evidence of systemic thrombo-embolism or a clot in LV but did not develop thrombo-embolism. The study period was December 1999 to November 2004 with follow-up available for a mean of 27.6 months. Patients who presented with thrombo-embolism (n = 28) formed group A, and those who developed evidence of thrombo-embolism during the hospital stay (n = 17) formed the group B. Another 5 patients were found to have an LV thrombus but did not develop thrombo-embolism (Group C).

Comprehensive histories, physical examinations, laboratory investigations, and two-dimensional echocardiograms were performed on all patients during the initial evaluation and subsequent discharge as well as regular follow-up every at 4 to 6 weeks. The echocardiograms were performed by experienced cardiologists trained in paediatric echocardiography. Thrombus was defined by the presence of a distinct echogenic mass, identified in at least two different views and associated with regional or global wall-motion abnormality. All patients were anticoagulated with heparin initially and then Warfarin aiming an INR of 2.0 to 2.5.

A cerebrovascular accident was diagnosed by the clinical evidence of acute stroke, usually confirmed by neurological consultation. In all cases of stroke, brain imaging with CT was performed. The occurrence of peripheral arterial embolization was diagnosed by the development of acute extremity arterial occlusion, with confirmation by Doppler. Angiography was not performed in any patient. The management of underlying myocarditis was done by a standard protocol adopted in the unit. All hypothesis testing was two-tailed, and $p < 0.05$ was considered statistically significant.

Results:

Of all admissions to the paediatric cardiology unit over the 5 year study period, myocarditis and dilated Cardiomyopathy was the underlying lesion in 405 patients. Of these 50 patients (12.3%) had evidence of thrombo-embolism. The mean age of patients was 2.1 ± 4 years. The male to female ratio was 1.5:1. Baseline characteristics were similar for patients with and without LV thrombi. No patient had a prior diagnosis of stroke or peripheral embolic event.

Table I: Clinical Presentation

Clinical symptoms	n=	%age
Hemiplegia	35	78
Hemipresis	08	18
Monopresis	02	04
Fits	05	11
Unconsciousness	01	02
Transient blindness	01	02

Systemic embolism was the presenting feature in 28 (6.9%) patients (Group A) while another 17 (4.2%) developed it during the hospital stay (Group B). Another 5 patients had thrombus in the LV but did not develop embolism. The groups were similar with respect to other baseline characteristics, co-morbid illnesses, and drug therapies other than anticoagulants (Table 1).

Table 2. Echocardiographic Factors

Factors	Group A (n=28)	Group B (n=17)
LVIDD	40.0±11	41.4±9.9
Clot in L.V.	06	03
EF, %	6.5±5.5	16.0±6.9
FS, %	07±3.5	08(18.1)
Pericardial effusion	01	02
Clot in LA	-	01

Table: 3.Outcome

Group (Number)	Recovery	Death
Group A (28)	12	02
Group B (17)	07	02
Group C (05)	02	-

Two dimensional echocardiography variables: All 50 patients showed seriously impaired LV function with mean ejection fraction (EF) for those with vs. those without thrombo-embolism was 17.5 ± 5.5 vs. 20.0 ± 6.9 ($p = 0.08$). LVEDD was higher in patients with thrombo-embolism compared with those who did not but was not statistically significant (Table 2). Two dimensional echocardiography showed abnormal right ventricular systolic fraction in some children with dilated Cardiomyopathy. This may result from the myopathic process involving the right heart or may be secondary to dysfunctional septal motion from an increased left ventricular end diastolic pressure. None of our patients had an evidence of a clot in right ventricle. Involvement of right ventricle was associated with poor outcome in terms of recovery but had no correlation with the incidence of thrombo-embolism. TD imaging which has recently been implicated as an important predictor of outcome in patients with dilated Cardiomyopathy was not investigated.

Embolic events and survival: In group A, 26/28 patients presented with a stroke. Only 6 had a thrombus in LV at the time of admission. None of these patients was taking warfarin or Aspirin, prior to the episode of thrombo-embolism. All 28 patients with or without LV thrombus were treated with heparin and then oral anticoagulant warfarin and antiplatelet dose Aspirin. There were two deaths.

In group B, only 3/17 patients had thrombus in the LV on echocardiography at presentation. Of remaining 14, 8 were started anticoagulation but still went on to develop a stroke. Ten out of 17 patients were known patients with myocarditis or dilated Cardiomyopathy and were already taking Aspirin in antiplatelet dose. None of these patients was on Warfarin. There were 2 deaths in this group as well (Table 3).

At a mean follow-up period of 27.6+14.9 months, data was available for only 34 patients (68%). There were

no further deaths and all 31 patients with a stroke showed some variable recovery. None of them showed a full functional recovery but majority 22/31 (71%), were in good functional status. Heart transplantation is not an option in our setup and none of the patients went overseas to seek this option.

Discussion:

The incidence of LV thrombus and thrombo-embolism in patients with myocarditis and dilated Cardiomyopathy was 12.1%, similar to rates of 11 to 44% published in the literature[11-14]. A poorly contracting ventricle allows blood stasis, which can lead to thrombus formation and subsequent embolization. The annual risk of systemic embolization in patients with dilated Cardiomyopathy reported in adults is 1.4 to 12.0%[15]. Mobile and protruding thrombi are thought to carry the highest risk[16]. Anticoagulation may reduce the chance of embolic events, but there is controversy about the necessity of routine anticoagulation in all patients with dilated Cardiomyopathy[17]. Several case-control studies and small prospective cohorts have produced mixed results and recommendations regarding the use of chronic anticoagulation in these patients in adults[15, 18-21].

Most of the studies that have examined the incidence of LV thrombus and thrombo-embolism in dilated Cardiomyopathy involved small numbers of patients. Earlier autopsy studies reported a very high frequency of thrombo-embolic events, ranging from 37 to 50%[14,22]. Fuster et al[11] in a retrospective study of 104 patients with nonischemic dilated Cardiomyopathy, reported an 18% frequency of thrombo-embolic events in patients not taking warfarin and an incidence of four clinically apparent events per 100 patient-years. More recent studies reported a lower incidence of thrombo-embolic events ranging from 1.7/100 to 3.2/100 patient-years in patients with severe LV dysfunction[19-21].

In the Vasodilators in Heart Failure Trial, the incidence of thrombo-embolism was 2.5/100 patient-years and did not differ between patients receiving anticoagulation and those not receiving anticoagulation[23] Ciaccheri et al[15], found an 11% prevalence of LV thrombus in patients with nonischemic dilated Cardiomyopathy, with no relation between the presence of intracavitary thrombus and systemic embolization. In the Survival and Ventricular Enlargement Trial, the incidence of stroke was 1.5/100 patient-years and the risk was higher in older patients with lower EF[10, 24]. In the Studies of Left Ventricular Dysfunction Trial, the results were similar, except for the fact that women were found to be at increased risk for thrombo-embolic events when compared to men[25].

We found that LVIDD was independent predictors of LV thrombus formation. There was a consistent, graded relationship between increasing chamber size and presence of LV thrombus. There was no significant association between LV thrombus and age of the patient. Kalaria et al[26] have reported an inverse relationship between severity of MR and the formation of LV thrombus. We did not find such correlation in our study. However, that report did not report any association between LV chamber size and LV thrombus.

In our study, lower EF was an independent predictor of systemic embolism in patients with and without LV thrombi. This supports the concept that this predictor is operative in patients in whom an LV thrombus cannot yet be identified. These findings are consistent with subgroup analysis from the Survival and Ventricular Enlargement Trial, in that patients with lower EF were reported to have higher rates of subsequent stroke during follow-up[10,24]. There was a trend toward significance in the association between increasing chamber size and peripheral thrombo-embolism irrespective of the presence or absence of LV thrombus.

We found that patients on antiplatelet dose of Aspirin also suffered an embolic event in Group B where the diagnosis of myocarditis or dilated Cardiomyopathy was already known. In addition, the occurrence of an embolic event, rather than the echocardiographic finding of LV thrombus, had an important bearing on outcome. This implies that any anticoagulant therapy, if it is to impact on survival, probably should be given preemptively, before the appearance of a thrombus on echocardiography[27].

In summary, in patients with myocarditis or dilated Cardiomyopathy, markedly dilated LV chamber size with lower EF appears to be at particularly high risk for LV thrombus formation and subsequent thrombo-embolism. All patients with EF below 20% should be treated with prophylactic anticoagulation in addition to anti platelet dose of Aspirin.

Presented in part at the 38th Annual meeting of the Association of the European Paediatric Cardiology, Porto, Portugal, May 27, 2002.

Reference

1. Friman G; Wesslen L; Fohlman J; Karjalainen J; Rolf C.The epidemiology of infectious myocarditis, lymphocytic myocarditis and dilated Cardiomyopathy. *Eur Heart J* 1995 ;16 Suppl O:36-41.
2. Ho, KK, Pinsky, JL, Kannel, WB, et al (1993) The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 22(Suppl A),6-13
3. Gottdiener, JS, Gay, JS, Van Voorhees, L, et al (1983) Frequency and embolic potential of left ventricular thrombus in dilated Cardiomyopathy: assessment by two-dimensional echocardiography. *Am J Cardiol* 52,1281-1285
4. Reeder, GS, Tajik, AJ, Seward, JB (1981) Left ventricular mural thrombus: two dimensional echocardiographic diagnosis. *Mayo Clin Proc* 45,82-86
5. Khadra, AS, Salem, DN, Rand, WM, et al (1998) Warfarin anticoagulation and survival: a cohort analysis from the studies of left ventricular dysfunction. *J Am Coll Cardiol* 31,749-753

6. Williams, JF, Jr, Bristow, MR, Fowler, MB, et al (1995) Guidelines for the evaluation and management of heart failure: report of the American College of Cardiology/American Heart Association Task Force on Practical Guidelines (Committee on Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 26,1376-1398
7. Laupacis, A, Albers, G, Dunn, M, et al (1992) Antithrombotic therapy in atrial fibrillation. *Chest* 102(Suppl),S426-S433
8. Falk, RH (1990) A plea for a clinical trial of anticoagulation in dilated Cardiomyopathy. *Am J Cardiol* 65,914-915
9. Koniaris, LS, Goldhaber, SZ (1998) Anticoagulation in dilated Cardiomyopathy. *J Am Coll Cardiol* 31,745-748
10. Loh, E, Sutton, MS, Wun, CC, et al (1997) Ventricular dysfunction predicts stroke following myocardial infarction. *N Engl J Med* 336,251-257
11. Fuster, V, Gersh, BJ, Giuliani, ER, et al (1981) The natural history of idiopathic dilated Cardiomyopathy. *Am J Cardiol* 47,525-530
12. Cheng, JW, Spinler, SA (1994) Should all patients with dilated Cardiomyopathy receive chronic anticoagulation? *Ann Pharmacother* 28,604-609
13. Wilensky, RL, Jung, SC (1995) Thrombo-embolism in patients with decreased left ventricular function: incidence, risk, and treatment. *J Cardiovasc Risk* 2,91-96
14. Roberts, WC, Siegel, RJ, McManus, BM (1987) Idiopathic dilated Cardiomyopathy: analysis of 152 necropsy patients. *Am J Cardiol* 60,1340-1355
15. Ciaccheri, M, Castelli, G, Cecchi, F, et al (1989) Lack of correlation between intracavitary thrombosis detected by cross-sectional echocardiography and systemic emboli in patients with dilated Cardiomyopathy. *Br Heart J* 62,26-29
16. Fuster, V, Halperin, JL (1989) Left ventricular thrombi and cerebral embolism. *N Engl J Med* 320,392-394
17. Stevenson, LW, Perloff, JK (1988) The dilated cardiomyopathies: clinical aspects. *Cardiol Clin* 6,197-218
18. Stratton, JR, Nemanich, JW, Johannessen, KA, et al (1988) Fate of left ventricular thrombi in patients with remote myocardial infarction or idiopathic Cardiomyopathy. *Circulation* 78,1388-1393
19. Natterson, PD, Stevenson, WG, Saxon, LA, et al (1995) Risk of arterial embolization in 224 patients awaiting cardiac transplantation. *Am Heart J* 129,564-570
20. Falk, RH, Foster, E, Coats, MH (1992) Ventricular thrombi and thrombo-embolism in dilated Cardiomyopathy: a prospective follow-up study. *Am Heart J* 123,136-142
21. Katz, SD, Marantz, PR, Biasucci, L, et al (1993) Low incidence of stroke in ambulatory patients with heart failure: a prospective study. *Am Heart J* 126,141-146
22. Spodick, DH, Littmann, D (1958) Idiopathic myocardial hypertrophy. *Am J Cardiol* 1,610-623
23. Dunkman, WB, Johnson, GR, Carson, PE, et al (1993) Incidence of thrombo-embolic events in congestive heart failure: the V-HeFT VA Cooperative Studies Group. *Circulation* 87(6Suppl),VI94-VI101
24. Pfeffer, MA, Braunwald, E, Moye, LA, et al (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 327,669-677
25. Dries, DL, Rosenberg, Y, Waclawiw, M, et al (1997) Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials. *J Am Coll Cardiol* 29,1074-1080
26. Kalaria, VG, Passannante, MR, Shah, T, et al (1998) Effect of mitral regurgitation on left ventricular thrombus formation in dilated Cardiomyopathy. *Am Heart J* 135,215-220
27. Gunthard J, Stocker F, Jaggi E, Oberhansli I, Wyler F. Dilated Cardiomyopathy and thrombo-embolism. *Eu J Pediatr* 1997;156:3-6.
28. Sadiq M, Alvi Y, Arifi MA, Khan A, Haq SU. Pattern of heart disease in children presenting to a paediatric tertiary referral centre. *Pak Pediatr J*1999; 23 (4): 125-30.