

Arterial stiffness during acute and recovery phases of children with rheumatic fever

Nik Nor Izah Nik Ibrahim, MB.BCh.BAO (Dublin)*, Hayati Jaafar, MMed (Paeds) (USM)**, Aida Hanum Ghulam Rasool, PhD*, Abdul Rahim Wong, MRCP (UK)***

*Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, **KPJ Kluang Utama Specialist Hospital, Kluang, Johor and ***Department of Paediatrics, Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan

SUMMARY

Acute rheumatic fever (ARF) is associated with systemic inflammation and arterial stiffness during the acute stage. It has not been reported if arterial stiffness remains after recovery. The aim of this study was to determine the arterial stiffness during acute stage and 6 months after recovery from ARF. Arterial stiffness was assessed by carotid femoral pulse wave velocity (PWV) in 23 ARF patients during the acute stage of ARF and 6 months later. Simultaneously, erythrocyte sedimentation rate (ESR) and other anthropometric measurements were taken during both stages. There was a significant reduction in PWV; 6.5 (6.0, 7.45) m/s to 5.9 (5.38, 6.48) m/s, $p=0.003$ 6 months after the acute stage of ARF. Similarly, ESR was also significantly reduced from 92.0 (37.5, 110.50) mm/hr to 7.0 (5.0, 16.0) mm/hr, $p=0.001$. In conclusion, arterial stiffness improved 6 months after the acute stage with routine aspirin treatment; this correlates well with the reduction in systemic inflammation.

KEY WORDS:

Acute rheumatic fever, arterial stiffness, pulse wave velocity, erythrocyte sedimentation rate

INTRODUCTION

Acute rheumatic fever (ARF) and its sequelae rheumatic heart disease (RHD) remains a significant health problem in developing countries and continues to be a major cause of morbidity and mortality among young people. In Malaysia, the reported incidence of ARF between 1981-1990 was 15.8/100,000.¹ Its pathogenesis has been linked to post infectious group A β haemolytic streptococcal pharyngitis. The inflammation that is present in the early stages of ARF may lead to changes in arterial wall properties causing endothelial dysfunction and arterial stiffness. The presence of arterial stiffness in children with ARF has previously been reported.² However, whether arterial stiffness remains after recovery has not been investigated.

Arterial stiffness measured through carotid-femoral pulse wave velocity (PWV) is an independent predictive marker of cardiovascular disease. Carotid-femoral PWV has been shown to improve in children with mitral stenosis after surgical intervention.³ To our knowledge, there is no long

term follow up study on the progress of arterial stiffness in ARF children after the infection has resolved. This study aimed to determine arterial stiffness during the acute and recovery phases of children presenting with ARF.

METHODOLOGY

This was a prospective cohort study comparing arterial stiffness among ARF children during the acute episode of ARF and 6 months later. The study was conducted between January 2008 and July 2010.

This study was approved by the Ethical Committee of Hospital Universiti Sains Malaysia (HUSM). Written informed consent was obtained from patients' caregivers and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients diagnosed with acute rheumatic fever based on the Modified Duckett-Jones Criteria 2003 were enrolled. The exclusion criteria were patients with chronic illnesses such as thalassaemia, leukaemia, bronchial asthma, congenital heart disease, autoimmune disease and patients who were on anti-inflammatory medication other than the treatment for ARF. Patients below 10 years were also excluded as the assessment of arterial stiffness required patients' cooperation and ability to stay still.

Study protocol

The patients' demographic data, baseline anthropometric measurements and detailed history were obtained for each participant. All ARF patients received aspirin 80-100 mg/body weight in divided doses for at least 6 weeks. Those with carditis were also treated with frusemide and captopril. Blood for complete blood count, erythrocyte sedimentation rate (ESR) and antistreptolysin O titre (ASOT) were taken. Patients were assessed for arterial stiffness non-invasively via the parameter carotid femoral PWV using arterial tonometer and the SphygmoCor device (AtCor Medical, Australia).

Carotid femoral PWV measures the velocity of the pressure waveform between the femoral and carotid arteries; it is a widely used parameter to assess arterial stiffness. It is calculated by measuring the pulse transit time and the distance between the two sites. The velocity of the blood pressure waveform is dependent on the stiffness of the artery

This article was accepted: 27 December 2015

Corresponding Author: Nik Nor Izah Nik Ibrahim, Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

Email: izah@usm.my

Table I: Arterial stiffness, ESR and other clinical indices during acute stage of ARF and 6 months after

| | Acute stage ARF | 6 months follow-up | p |
|--------------|-----------------|--------------------|-------|
| ASOT (IU/mL) | 200 (0,400) | 100 (0,250) | 0.004 |
| ESR (mm/HR) | 92 (37.5,110.5) | 7.0 (5.0,16.0) | 0.001 |
| PWV (m/s) | 6.5 (6.0,7.45) | 5.9 (5.38, 6.48) | 0.003 |
| SBP (mmHg) | 104 (96,116) | 110 (104,114) | 0.509 |
| DBP (mmHg) | 58 (55,64) | 62 (56,67) | 0.271 |

ARF = acute rheumatic fever; ASOT = anti-streptolysin O titre; ESR = erythrocyte sedimentation rate; PWV = pulse wave velocity; SBP = systolic blood pressure; DBP = diastolic blood pressure

along which the pulse is travelling. A higher value of carotid femoral PWV indicate aortic stiffness and vice versa.

Two measurements were taken and average values were recorded; all measurements were performed by a single investigator.

All patients were then followed up at 6 months and measurements of arterial stiffness, ESR, ASOT and blood pressure were repeated.

Data analyses

Statistical analysis was performed using the statistical package for social sciences (SPSS) software version 20 (SPSS Inc., Chicago, USA). Paired t-test or the non-parametric equivalent (Wilcoxon signed-rank test) was used to evaluate the changes in PWV, ESR, ASOT, SBP and DBP between acute stage and at 6 months. Statistical significance was inferred at $p < 0.05$. Results were presented as mean \pm SD or median (IQR).

RESULTS

Twenty three patients with ARF fulfilling the inclusion and exclusion criteria were recruited (15 males, 8 females). Out of these, 17 had carditis and 6 did not. The mean age and BMI of the patients were 11.35 ± 1.53 kg/m² and 16.24 ± 3.72 kg/m² respectively. There was no significant difference in the baseline characteristics between the carditis and non carditis group.

PWV were compared during acute stage ARF and 6 months later. As shown in Table I, there was a significant reduction in PWV [6.5 (6.0, 7.45) m/s to 5.9 (5.38, 6.48) m/s, $p=0.003$]. Similarly, ESR was also significantly reduced [92 (37.5, 110.50) mm/hr to 7.0 (5.0, 16.0) mm/hr, $p=0.001$].

DISCUSSION

This study demonstrated that arterial stiffness as measured by PWV improved after the acute phase of ARF. This is associated with marked reduction in systemic inflammation as shown by the blood ESR parameter. No change was seen in blood pressure during the acute phase and 6 months later.

An increased arterial stiffness in patients with ARF has previously been reported.^{2,3} Our study showed that arterial stiffness in ARF improved, as reflected by the decrease in PWV (thus the reduction in arterial stiffness) in affected patients 6 months later. On further analysis, the reduction in arterial stiffness was significant in both groups, those with carditis as well as those without carditis.

Abnormal autoimmune host response to specific streptococcal antigen in ARF has been associated with the development of inflammation and may rarely proceed to vasculitis. Evidence suggests that the antibody against group A carbohydrate reacts with valve endothelium protein leading to eventual scarring, valvular injury and carditis. Similar immune response may have occurred in the endothelium of large vessels which is reflected by the changes in systemic arterial wall properties in the form of endothelial dysfunction and arterial stiffness. However, long term follow up of these ARF patients in our study showed that arterial stiffness improved as the acute phase resolved. To our knowledge, this is the first study looking at the changes in arterial stiffness in patients with ARF during an acute attack and 6 months later. Our study thus suggests that ARF is associated with short term change in systemic arterial haemodynamics without long term sequelae. It was recently reported by Ozdogru³ that arterial stiffness in children with mitral stenosis improved after undergoing valvuloplasty procedure. We further support this finding that even in ARF patients without any mechanical intervention, the arterial stiffness still improved. In contrast with Kawasaki disease that also involves immunological aetiology, the arterial stiffness was reported to persist even after the acute phase.⁴ However, the underlying pathology of Kawasaki disease is dissimilar; where vasculitis is a key feature. Moreover, the treatment regime also differs from ARF; the duration of aspirin use is also often shorter than in ARF.

The reduction in arterial stiffness was accompanied by a reduction in ESR which is the inflammatory marker routinely assessed in ARF. This further supports our finding that the inflammation in ARF is transient and once the inflammation settled, arterial stiffness also improved. The pathogenesis of arterial stiffness is very much related to the role of inflammation.

In this study, all patients were given a routine treatment of aspirin with an additional treatment of frusemide and captopril for patients with carditis. Aspirin which is a cyclo-oxygenase inhibitor and non-steroidal anti-inflammatory may play a role in reducing the inflammation and improving the arterial stiffness of patients.⁵ Similarly, there have been many reports that ACE inhibitors improve arterial stiffness independent from any changes in blood pressure.⁶

CONCLUSION

This study demonstrated that an improvement in arterial stiffness in children with ARF was seen 6 months after the acute phase following a routine aspirin treatment. This improvement correlates well with the reduction in systemic inflammation.

ACKNOWLEDGEMENT

This study was supported by the Fundamental Research Grant Scheme (FRGS) from the Ministry of Education of Malaysia (Grant no. 203/PPSP/6171003)

REFERENCES

1. Omar A, Pattern of acute rheumatic fever in a local teaching hospital. *Med J Malaysia* 1995; 50(2): 125-30.
2. Ciftel M, Yilmaz O, Kardelen F, *et al.* Carotid intima media thickness and arterial stiffness in children with acute rheumatic fever. *Pediatr Cardiol* 2014; 35(1): 16-21.
3. Ozdogru I, Celik A, Dogan A, *et al.* Improved arterial stiffness in mitral stenosis after successful percutaneous balloon valvuloplasty. *Cardiol J* 2012; 19(6): 586-90.
4. Cheung YF, Wong SJ, Ho MH. Relationship between carotid intima-media thickness and arterial stiffness in children after Kawasaki disease. *Arch Dis Child* 2007; 92(1): 43-7.
5. Pietri P, Vlachopoulos C, Terentes-Printzios D, *et al.* Beneficial effects of low-dose aspirin on aortic stiffness in hypertensive patients. *Vasc Med* 2014; 19(6): 452-7.
6. Asmar R. Effect of antihypertensive agents on arterial stiffness as evaluated by pulse wave velocity: clinical implications. *Am J Cardiovasc Drugs* 2001; 1(5): 387-97.