Left ventricular dysfunction in sickle cell disease: the value of an electrocardiographic marker of increased risk of arrhythmia

Sickle cell disease is one of the most prevalent genetic diseases worldwide; affecting 1/400 individuals of African descent as well as people of Arab, Indian and Hispanic descents.1-3 Abnormalities of cardiovascular function have increasingly been documented in sickle cell disease patients. Reports from several clinical studies in recent times have drawn attention to some ‘emerging’ cardiac pathologies in sickle cell disease and their potentially negative impact on cardiovascular function in these patients. Among these are myocardial infarction without coronary artery disease, pulmonary hypertension and cor pulmonale.4 Moreover, sudden unexpected death has become increasingly recognised as an important clinical feature of both the homozygous and heterozygous sickling syndromes; although the exact nature and its cause has remained unexplained.5-10

The emergence of cardiac complications in sickle cell disease patients could be attributed to the increasing life expectancy observed in these patients. Recent data indicates that 86 to 90% of patients survive to beyond 20 years of age.11 With the continued development of improved management and supportive care for patients with sickle cell anaemia and the resultant increase in life span, the spectrum of cardiac dysfunction is likely to enlarge in the future.

The mechanism underlying cardiac dysfunction in sickle cell anaemia has been extensively studied and multiple mechanisms have been proposed. In addition to the impaired microvascular circulation from intravascular plugs of sickled erythrocytes, other contributory factors include: extensive fibromuscular dysplastic narrowing of small cardiac arteries, non-inflammatory focal degeneration and apoptosis, platelet abnormalities or similar stimuli for endothelial and smooth muscle proliferation.12-14 The hyperkinetic circulation as a result of chronic anaemia contributes to eccentric ventricular hypertrophy and cardiomegaly, and the severity of cardiac chamber dilatation progresses with increasing anaemia.15 Despite myocardial remodelling/ hypertrophy, the patients have increased myocardial wall stress as well as impaired ventricular relaxation.16

Data from clinical studies evaluating left ventricular systolic function using load-independent measures of myocardial contractility have revealed significant systolic dysfunction in sickle cell anaemia patients.17,18 The development of left ventricular systolic and/or diastolic dysfunction in sickle cell anaemia is associated with increased morbidity and mortality.19 There is a large body of evidence showing that diastolic dysfunction in sickle cell disease contributes to pulmonary hypertension and represents an independent predictor of mortality in these patients.19

It has been recognised that ischaemic phenomena associated with sickle cell anaemia could elicit morphological and functional abnormalities in the cardiac conducting system, resulting in paroxysmal arrhythmia and could further worsen the ventricular dysfunction.2 Such electrical instability induced by myocardial ischaemia has been postulated to be the cause of sudden cardiac death in patients with sickle cell disease.2,3

In the presence of left ventricular diastolic dysfunction, atrial fibrillation and indeed any form of arrhythmia causes significant cardiac decompensation. Atrial fibrillation in sickle cell disease is believed to be due to increase in atrial size with accompanying advanced atrial remodelling and profound global electrophysiological changes in refractoriness. Additional factors affecting atrial refractoriness include autonomic impairment, scars, and changes in the cellular membrane function.16 Several non-invasive electrocardiographic indicators have been investigated to predict the occurrence of arrhythmia in left ventricular diastolic dysfunction. On a 12-lead surface electrocardiogram, P-wave dispersion, because of its relationship to the non-homogenous and interrupted conduction of sinus impulses both intra- and interatrially, is recognised as a non-invasive marker of risk of atrial fibrillation.21

In the light of this, one pertinent question needs to be addressed: what is the clinical utility of P-wave dispersion in sickle cell anaemia? A step towards unravelling this puzzle would involve the examination of the relationship between P-wave dispersion and measures of left ventricular function in sickle cell anaemia patients, and the comparison of the indices with those of appropriately matched controls. In this connection, the article in this issue, ‘P-wave dispersion: relationship to left ventricular function in sickle cell anaemia’ is of relevance. The authors showed that P-wave duration and P-wave dispersion were significantly increased in sickle cell anaemia and that P-wave dispersion had a negative correlation with indices of left ventricular diastolic function. This novel study provides an interesting insight into the potential value of this simple electrocardiographic tool in the evaluation of ventricular function in sickle cell anaemia. This is especially useful in resource-limited areas of developing countries where access to modern investigative modalities is lacking. Major challenges in the use of this tool are the difficulty in standardisation of methods and the lack of acceptable normal limits of P-wave dispersion in the general population.

It is expected that this pilot study will stimulate further research efforts to determine the diagnostic/normal cut-off values, and specificity and sensitivity, as well as the long-term prognostic significance of increased P-wave dispersion in sickle cell disease.

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References
1. Ronald LN. Origins and dispersion of sickle cell gene. In: Embury SH, Hebbel RP, Mohandas N, Steinberg MH (eds). Sickle Cell Disease: Basic Principles and Practice, 4th edn. New York: Raven Press, 1994: 353–377.
2. Hickman M, Modell B, Green Gross P Mapping the prevalence of sickle cell and thalassaemia in England: Estimating and validating ethnic-specific rates. Br J Haematol 1999; 104: 860–867.
3. Serjeant GR, Serjeant BE, Forbes M, Hayes RJ, Higgs DR, Lehman H. Haemoglobin gene frequencies in the Jamaican population: a study of 100,000 newborns. Br J Haematol 1986; 64: 253–262.
4. Mc Cormick WK. Massive nonatherosclerotic myocardial infarction in sickle cell anaemia. Am J Forensic Med Pathol 1988; 9: 151–154.
5. Gerry J, Bukley B, Hutchins G. Clinicopathological analysis of cardiac dysfunction in 52 patients with sickle cell anaemia. Am J Cardiol 1978; 42: 211–216.
6. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004; 350: 886–895.
7. Collins FS, Orringer EP. Pulmonary hypertension and cor pulmonale in the sickle haemoglobinopathies. Am J Med 1982; 73: 814–821.
8. Kart JA, Coffey SE, Estella E, Robinowitz M, Posey DM, Virmani R. Comparison of sudden death syndromes with and without sickle cell trait. Blood 1989; 74(suppl 1): 62.
9. Liesner RT, Vandenbergh EA. Sudden death in sickle cell disease. J R Soc Med 1993; 86: 484–485.
10. James TN, Riddick L, Massing GK. Sickle cells and sudden death: morphologic abnormalities of the cardiac conducting system. J Lab Clin Med 1994; 124: 507–520.
11. Platt OS, Brambilla OJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Eng J Med 1994; 330: 1639–1644.
12. Keiden AJ, Sower MC, Johnson CS, Noguchi CT, Girling AJ, Steven SME, Stuart J. Effect of polymerization tendency on haematological, rheological and clinical parameters in sickle cell anaemia, Br J Haematol 1989; 71: 551–557.
13. James TN. Morphological characteristics and functional significance of focal fibromuscular dysplasia of small coronary arteries. Am J Cardiol 1990; 65: 129–229.
14. Frenette PS. Sickle cell vaso-occlusion: multistep and multicellular paradigm. Curr Opin Haematol 2002; 9: 101–106.
15. Balfour IC, Covitz W, Davis H, Rao PS, Strong WB, Alpert BS. Cardiac size and function in children with sickle cell anaemia. Am Heart J 1984; 108: 345–350.
16. Adebayo RA, Balogun MO, Akinola NO, Akintomide AO, Asaley C.M. Non-invasive assessment of cardiac function in patients with sickle cell anaemia. Trop Cardiol 2004; 30(120): 51–55.
17. Colan SD, Borow KM, Neumann A. Left ventricular end-systolic wall stress – velocity of fibre shortening relation: a load-independent index of continued on page 66…

From the Editor’s Desk

The Cardiovascular Journal of Africa (CVJA) is making great strides but faces considerable challenges. It is now well accredited in all of the major databases in the world and is widely read. The increase in readership over the past year was 33% and 3 000 articles are downloaded monthly via Pubmed LinkOut. This reflects usage of only four years of the CVJA, which has a dataset of 400 full-text articles in Pubmed.

However, we are facing a bottleneck due to insufficient appropriate reviewers for the submitted articles, and this is causing a delay in publishing these articles. It appears that South African reviewers take greater pride in reviewing articles for overseas authors. The CVJA is as well rated as any foreign journal. We are now as a matter of policy also registering authors as reviewers.

Please note that because of the backlog in published articles we have provided authors with the opportunity to publish ahead of print. This implies that your article will appear in an electronic version such as PubMed and elsewhere. There will, however, be an additional charge of R1 000 for African authors and R3 000 for overseas authors.

We now have CrossCheck available to check for any suspected plagiaristic articles.

Ek wil graag outeurs nooi om ook wetenskaplike werk voor te lê vir publikasie in CVJA in Afrikaans of ander inheemse Afrika tale. Dit sal gelyke aandag geniet as die engelse artikels met dieselfde soort erkenning en verspreiding. Die tydskrif wil baie toekenningswerk op te skryf. Ons oorweeg tans ‘n toekenning vir ‘n artikel wat in Afrikaans of ‘n inheemse taal geskryf is en toepaslik is vir Afrika siektes en omstandighede.

Indien daar geen eweknie beoordeelaars (peer reviewers) beskikbaar is vir ‘n bepaalde artikel, word die manuskript terug gestuur aan die outeur.

If no reviewers are available for reviewing the article, it will unfortunately have to be sent back to the author.

We thank the following South Africans who reviewed articles for the CVJA during 2010: Julia Aalbers, M Abelson, J Badenhorst, Piet Becker, Megan Bester, Paul Brink, Geoffrey Candy, R Chauke, Ashley Chin, Daneele Dietrich, Stefan du Plessis, Anna-Mart Engelbrecht, Rajiv Erasmus, Rafique Essop, M Faadiel Essop, Mieke Faber, Julia Goedecke, Vladimir Grigorov, Dave Harris, Mbuilu Jody, James Ker (jun), James Ker (sen), John Lawrenson, Melanie Louw, Leoné Malan, Maurice Mars, J Marx, Indres Moodley, M Mpe, Cephas Musabayane, M Ntsekhe, Andrzej Okreglicki, Brian Rayner, Paul Rheeder, Saartjie Roux, Robert Schall, Aletta Schutte, R Scott-Millar, Y Seedat, Brandon Shaw, Karen Sliwa, Jan Smedema, Cornelius Smuts, Harris Steinman, Kristela Steyn, Nicky Sulzer, H Theron, Nico van der Merwe, Lynette Zäuhlke, Makhosazane Zungu

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Editor-in-Chief (South Africa)
but it is important to highlight the multi-tribal orientation of the hospital as Cameroon is a country where the way someone is treated could be determined by his/her tribal origin, depending if that tribe is well represented or not in society.

We also found that congenital heart diseases were predominant in the Banto and Bamileke people. However, this could be due to the fact that the majority of patients came from these regions, which are closest to the hospital. Bamileke are known to marry close relatives and therefore we could hypothesise that genetic background could be linked to the predominance of congenital heart diseases found in this tribe. However, unless scientifically proven, this must remain an assumption.

Since there are only a few cardiac centres in the country, and more importantly because patients cannot afford the cost of treatment, pre- and post-surgical follow up is very challenging. There is a need to establish programmes to better inform patients about their disease and the importance of proper follow up. More than 60% of children have a very poor academic background and almost the same percentage of rural parents do not have a secondary school education.

Long-term post-surgical death rate is estimated at 0.7% and the main cause of death is thought to be malignant arrhythmias occurring after correction of the congenital heart disease. In developed countries, particularly Europe and America, diagnosis and treatment of cardiac pathologies are readily affordable by most citizens through coverage by insurance plans. In the majority of developing nations, especially countries on the African continent, this is not yet the case.

Thanks to the positive partnership between St Elizabeth Catholic General Hospital, Policlinico San Donato in Milan, Tertiary Sisters of St Francis, Associazione Bambini Cardiopatici nel Mondo and Cuore Fratello, some hope is offered to patients and their families. The initiative of St Elizabeth Catholic General Hospital in supporting early detection, diagnosis, treatment and patient follow up is encouraging; however, public health involvement and better funding are required to cover the expenses so that all patients are afforded the opportunity to receive proper treatment in a timely manner.

Conclusion

The data showed that a wide range of congenital heart diseases were represented in the cardiac centre of St Elizabeth Catholic General Hospital, Shisong, situated in a sub-Saharan rural area of Africa, and that isolated ventricular septal defect was the most prevalent pathology. However, despite successful cardiac surgery and treatment, patient follow up remained a significant challenge.

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References

1. Brickner ME, Hills LD, Lange RA. Congenital heart disease in adults: 1. N Engl J Med 2000; 342: 256–263.
2. Hoffman JI. Incidence of congenital heart disease: I. Postnatal incidence. Pediatr Cardiol 1995; 3: 103–111.
3. Abena-Obama MT, Muna WFT, Leckpa JP, et al. Cardiovascular disorders in sub-Saharan African children: a hospital-based experience in Cameroon. Cardiologie trop 1995; 21: 5–11.
4. Tantchev Tecoumi JC, Ambassa JC, Butera G, Giamberti A. L’implication des organisations non gouvernementales dans les systèmes de santé des pays du Sud: l’exemple du Shisong Cardiac Centre. Pan Afr Med J 2009; 2: 4.
5. Métras D, Turquin H, Coulibaly AO, Ouattara K. Congenital cardiopathies in a tropical environment. Study of 259 cases seen at Abidjan from 1969–1976. Arch Mal Coeur Vaiss 1979; 72(3): 305–310.
6. Muna WF. The importance of cardiovascular research in Africa today. Etnh Dis 1993; 3(Suppl): S8–12.
7. Sani MU, Mukhtar-Yola M, Karaye KM. Spectrum of congenital heart disease in a tropical environment: an echocardiography study. J Natl Med Assoc 2007; 6: 666–669.
8. Bassili A, Mukhtar SA, Dabous NI, Saher SR, Mukhtar MM, Zakia A. Congenital heart disease among school children in Alexandria, Egypt: an overview on prevalence and relative frequencies. J Trop Pediatr 2000; 6: 357–362.
9. Bannerman CH, Mahalu W. Congenital heart disease in Zimbabwian children. Ann Trop Pediatr 1998; 1: 5–12.
10. El Haq AI. Pattern of congenital heart disease in Sudanese children. East Afr Med J 1994; 9: 580–586.
11. Ejjim EC, Ike SO, Amisoba BC, et al. Ventricular septal defects at the University of Nigeria Teaching Hospital, Enugu: a review of echocardiogram records. Trans R Soc Trop Med Hyg 2009; 103(2): 159–161, E-pub 2008 August 3.
12. Marelli AJ, Mackie AS, Ionescu-Ittu R, et al. Congenital heart disease in the general population: changing prevalence and age distribution. Circulation 2007; 115: 163–172.
13. Diop BB, Ba SA, Ba K, et al. Congenital cardiopathies: anato-mo-clinical, prognostic, and therapeutic features apropos of 103 cases seen at the Cardiology Clinic of the Dakar University Hospital Center. Dakar Med 1995; 2: 181–186.
14. Sulafa KM, Karanji Z. Diagnosis, management and outcome of heart disease in Sudanese patients. East Afr Med J 2007; 84(9): 434–440.
15. Ould Zein H, Ould Lebchir D, Ould Jiddou M, et al. Consultation of congenital heart diseases in pediatric cardiology in Mauritania. Tunis Med 2006; 84(8): 477–479.
16. Hammami O, Ben Salem K, Boujemaa Z, et al. Epidemiologic and clinical features of congenital heart diseases in children at the Bizerta Hospital. Tunis Med 2007; 10: 829–833.

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