MARCH / APRIL 2011
VOL 22 NO 2

CVJ AFRICA

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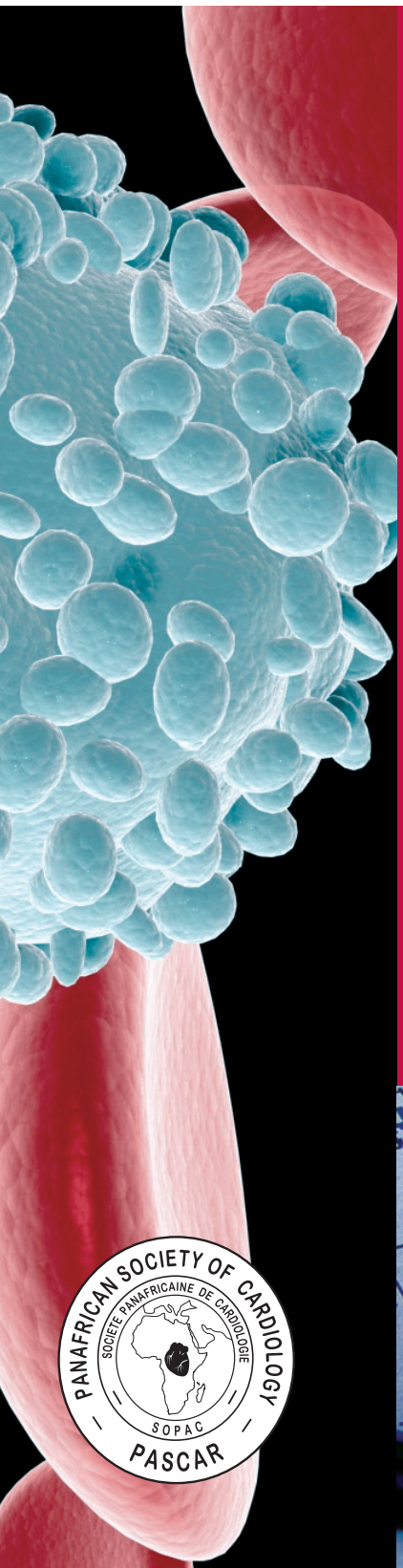

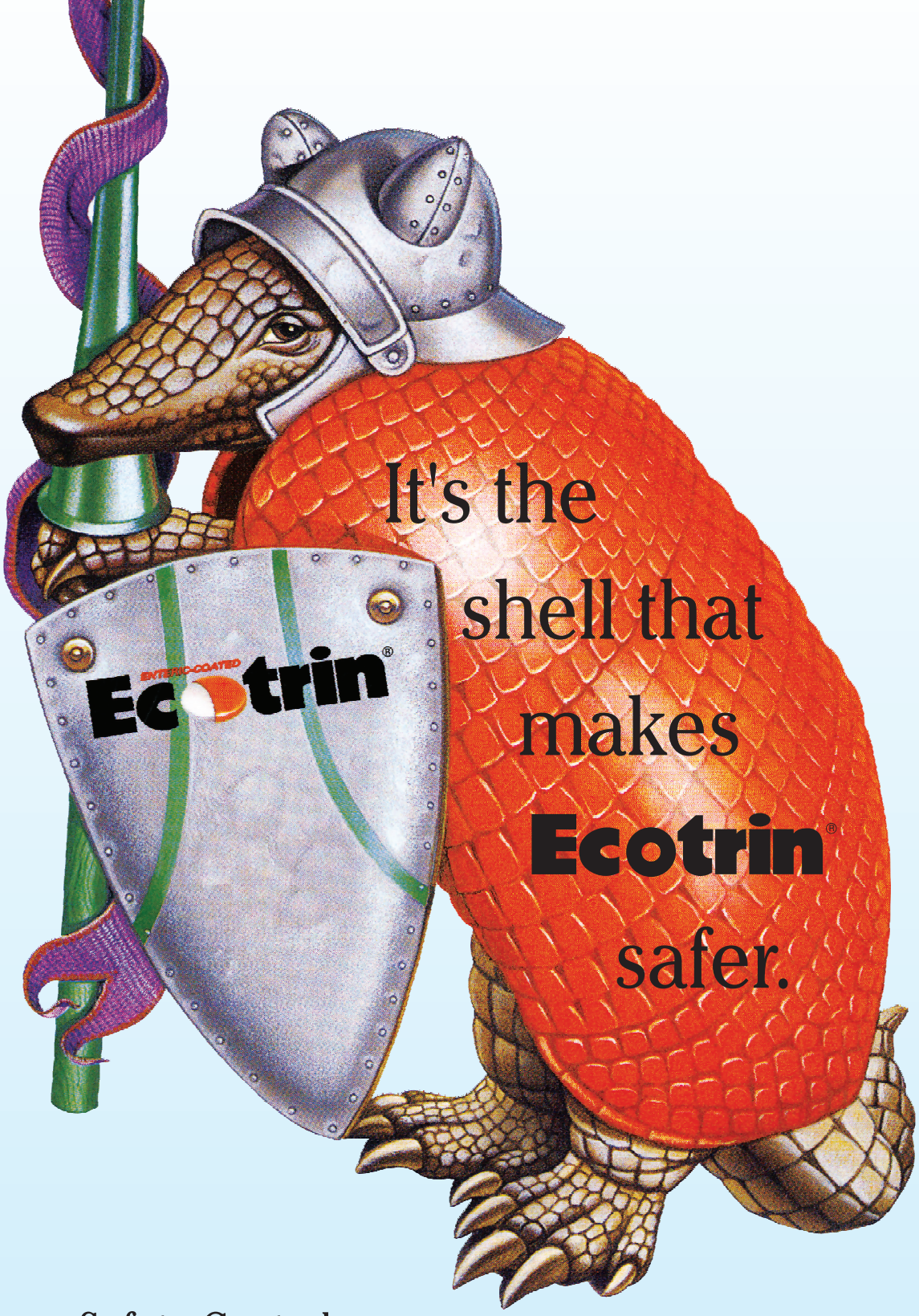

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ISSN 1995-1892 (print)
ISSN 1680-0745 (online)

CVJ AFRICA

Cardiovascular Journal of Africa | www.cvja.co.za

VOL 22, NO 2. MARCH / APRIL 2011

CONTENTS

INDEXED AT SCISEARCH (SCI), PUBMED AND SABINET

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All submissions to CVJA are to be made online via www.cvja.co.za

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Full text articles available on: www.cvja.co.za or via www.sabinet.co.za; for access codes contact jaalbers@icon.co.za

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Subscriptions for six issues:
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Editorial

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 include myocardial infarction without coronary artery disease, pulmonary hypertension and cor pulmonale.[4-7] 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.[8-10]

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.[5,15] 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.[5] Such electrical instability induced by myocardial ischaemia has been postulated to be the cause of sudden cardiac death in patients with sickle cell disease.[5,10]

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.[20] 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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continued on page 66…

From the Editor's Desk

The *Cardiocascular 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 foreign journals. 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 printed publications 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 plagiarism in 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 graag jonger navorsers op die gebied van hartsiektes aanmoedig om navorsingswerk 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 manuskrip 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:
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Cardiovascular Topics

Occurrence and pattern of congenital heart diseases in a rural area of sub-Saharan Africa

JC TANTCHOU TCHOUMI, G BUTERA, A GIAMBERTI, JC AMBASSA, JC SADEU

Summary

The extent of congenital heart disease in Cameroon remains largely unknown. The aim of this study was to determine the occurrence and pattern of congenital heart diseases in the Cardiac Centre of St Elizabeth Catholic General Hospital, situated in a rural area of Cameroon.

Methods: **Between November 2002 and November 2008, a population of 2 123 patients with suspected cardiac pathologies were consulted at St Elizabeth Catholic General Hospital referral cardiac centre. Of these patients, 292 subjects were recruited for the study, based on detection of (1) precordial murmurs and/or cardiomegaly on chest X-ray examination, or (2) congenital heart diseases on transthoracic Doppler echocardiography examination.**

Results: **Congenital heart diseases and inorganic murmurs were found in 95.5 and 4.5% of the patients, respectively. Congenital heart diseases included tetralogy of Fallot (26.1%), isolated ventricular septal defect (38.8%), atrioventricular cushion defect (7.3%), isolated atrial septal defect (2.8%), arterial duct cases (12.4%), common arterial trunk (1.3%), isolated stenosis of the pulmonary artery (2.6%), coarctation of the aorta (1.1%), congenital mitral valve regurgitation (1.2%), atresia of the triscupid valve (1.6%), double-outlet right ventricle (2.1%), anomalous pulmonary venous return (1.5%) and left isomerism (1.2%).**

Conclusion: **Our data show that there is a high occurrence of congenital heart disease in this hospital in a rural zone of sub-Saharan Africa and that isolated ventricular septal defect is the predominant pathology. Post-surgical follow up remains very challenging as many parents cannot afford their children's medical treatment or are generally not well educated.**

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Keywords: congenital heart diseases, sub-Saharan Africa, ventricular septal defect, Cameroon

Submitted 13/11/09, accepted 21/3/10

Cardiovasc J Afr 2010; **21**: 63–66 www.cvja.co.za

DOI: CVJ-21.033

Congenital heart disease is defined as an abnormality in the cardio-circulatory structure or function, which is either present at birth or appears much later in life. The prevalence and pattern of this group of disorders varies both within and between regions and countries.[1,2] However, the extent of its occurrence in Cameroon is largely unknown.[3]

In the majority of developing nations, and especially in most countries in the African continent, only a small and insignificant portion of the population can afford the cost of diagnosis, medical treatment and/or surgical correction of congenital heart diseases. The situation is even worse for those living in rural areas where access to basic healthcare is already a serious issue. Despite their wealth in natural resources, rural areas in developing countries are usually the poorest regions in terms of financial resources. These regions depend entirely on the availability of public health funding to finance and support their healthcare. Most of the time these funds do not reach them or are simply not provided.

The Shisong referral cardiac centre is specialised in both adult and paediatric cardiology and is part of Shisong's St Elizabeth Catholic General Hospital, located in a rural area of the north-west province of Cameroon. This geographic location strategically complies with the principal mission of this hospital, which is to provide healthcare support to economically deprived rural areas of the country.

Since November 2002, when the cardiac centre became operational, a significant number of patients have presented at the hospital and been treated for various pathologies.[4] Obviously, treatment and prevention of malaria and HIV, and vaccination programmes are top of the list of priorities for public health in Cameroon. However, in our personal experience to date, we know that in Cameroon there are a significant number of patients with diagnosed or undiagnosed congenital heart diseases who are helpless because of associated expensive treatment.

The only scientifically based approach to draw public health attention to the seriousness of the problem is to provide evidence-based data that support our observations. Currently, there are no epidemiological data available on the prevalence and management of congenital heart diseases in Cameroon, and only a limited number of published studies on rural areas

of sub-Saharan Africa.[5,6] Therefore, the aim of this study was to determine the occurrence and pattern of congenital heart diseases in the cardiac centre of St Elizabeth Catholic General Hospital, situated in a rural area of Cameroon.

Methods

The ethics committee of St Elizabeth Catholic General Hospital approved the study. Between November 2002 and November 2008, a population of 2 123 patients aged between two months and 41 years (mean: 10.03 ± 9.7 years) was seen in the cardiac centre for various pathologies. Patients with one or a combination of the following pathological features: precordial murmurs, past history of recurrent respiratory heart diseases, clinical indications of suspicious cardiopathy and/or cardiomegaly on chest X-ray examination (cardiothoracic index > 0.55) underwent further screening tests for detection of congenital heart diseases. A total of 292 patients (58.2% females and 41.8% males) were recruited for the study.

Initially, patients underwent clinical examination, followed by a comprehensive transthoracic Doppler echocardiogram using an Acuson 4–7 MHz. In addition, a complete two-dimensional echocardiography examination was performed according to the recommendations of the American Society of Echocardiography.

Depending on the pathology, patients diagnosed with congenital heart diseases were put on a surgical list for sanitary evacuation to a collaborative centre (Instituto Polyclinico San Donato) in Italy where corrections of pathology were performed. The Tertiary Sisters of St Francis and two other charity organisations, the Cuore Fratello and Associazione Bambini Cardiopatici nel Mondo, paid for treatments and all inccured costs. Upon returning to Cameroon, patients were followed up at the Shisong cardiac centre.

Fig. 1. Map of Cameroon showing the provincial areas as well as the neighbouring countries of the patients included in the study.

Statistical analysis

Values are expressed as mean ± standard deviation (SD) and statistical analyses were performed using the Student's *t*-test. SPSS 11 statistical analysis software was used for all analyses and a p-value ≤ 0.05 was considered significant.

Results

Two groups of patients were identified based on their diagnoses. The first group (95.5%) had an echocardiographic diagnosis of congenital heart disease (n = 279) and the second (4.5%) inorganic murmurs (n = 13).

There are 10 provincial regions in Cameroon and patients' geographic origins were distributed as follows (Fig. 1): north (Maroua and Garoua, n = 2), north-west (Bamenda, n = 80), littoral (Douala, Nkongsamba and Tiko, n = 89), central (Yaounde, n = 66), and west (Bafoussam, n = 28) regions. The remaining patients (n = 11) were from the other provinces and neighbouring countries such as Gabon (n = 1) and Nigeria (n = 3). In addition, there are also more than 260 tribes in Cameroon. The patients' tribal origins were (Table 1): Banso (35.3%), Bamileke (32.2%), Douala (12.7%), Haoussa (8.4%), Ewondo (5.4%), Bakweri (2.6%) and others (3.4%).

Of the 1 831 patients remaining out of the total patients consulting (2 123), 321 had rheumatic heart disease (RHD) while the rest had no heart-related pathologies.

TABLE 1. PATIENT DISTRIBUTION BY TRIBE, AND TRIBAL REPRESENTATION IN CAMEROON

Tribe	*Patients (%)*	*Tribal representation in Cameroon (%)*
Banso	35.3	12.8
Bamileke	32.2	18.3
Douala	12.7	13
Haoussa	8.4	20.2
Ewondo	5.4	17.6
Bakweri	2.6	8
Others	3.4	10.1

TABLE 2. PERCENTAGE DISTRIBUTION OF CONGENITAL HEART DISEASES PER PATHOLOGY (n = 279 PATIENTS)

Pathology	*Percentage (%)*
Isolated ventricular septal defect	38.8
Tetralogy of Fallot	26.1
Arterial duct	12.4
Atrioventricular cushion defect	7.3
Isolated atrial septal defect	2.8
Isolated stenosis of the pulmonary artery	2.6
Double-outlet right ventricle	2.1
Atresia of the triscupid valve	1.6
Anormalous pulmonary venous return	1.5
Common arterial trunk	1.3
Congenital mitral valve regurgitation	1.2
Left isomerism	1.2
Coarctation of the aorta	1.1

TABLE 3. PATHOLOGY DISTRIBUTION WITH REGARD TO PATIENT AGE AT THE TIME OF DIAGNOSIS

	Age		
Pathology	*2 months – 2 years (%)*	*2–5 years (%)*	*> 5 years (%)*
Isolated ventricular septal defect	22	14.8	2
Tetralogy of Fallot	10	13.1	3
Arterial duct	6	3.9	2.5
Atrioventricular cushion defect	5	2.3	-
Isolated atrial septal defect	0.9	1.1	0.8
Isolated stenosis of the pulmonary artery	0.9	1.2	0.5
Double-outlet right ventricle	1.8	0.3	-
Atresia of the triscupid valve	1.1	0.5	-
Anormalous pulmonary venous return	0.6	0.7	0.2
Common arterial trunk	0.8	0.5	-
Congenital mitral valve regurgitation	0.2	0.3	0.7
Left isomerism	0.4	0.8	-
Coarctation of the aorta	0.2	0.4	0.5

Transthoracic Doppler echocardiogram

Congenital heart diseases were distributed as follows (Tables 2, 3): tetralogy of Fallot (26.1%), isolated ventricular septal defect (38.8%), atrioventricular cushion defect (7.3%), isolated atrial septal defect (2.8%), arterial duct cases (12.4%), common arterial trunk (1.3%), isolated stenosis of the pulmonary artery (2.6%), coarctation of the aorta (1.1%), congenital mitral valve regurgitation (1.2%), atresia of the triscupid valve (1.6%), double-outlet right ventricle (2.1%), anomalous pulmonary venous return (1.5%) and left isomerism (1.2%).

There was a significantly ($p \leq 0.005$) high percentage of large isolated peri-membranous ventricular septal defects (85%) compared to restrictive (10.2%) and muscular (4.8%) defects. Complete atrioventricular cushion defects (63.5%) were also significantly higher ($p \leq 0.005$) than incomplete (39.5%) cushion defects. Combined pathologies, such as ventricular septal defect with isolated atrial septal defect were found in 1.8% ($n = 5$) of patients; ventricular septal defect with arterial duct in 2.1% ($n = 6$); ventricular septal defect with pulmonary valve stenosis in 8.9% ($n = 25$); and left isomerism with arterial duct in 1% ($n = 3$) of cases.

Pre- and post-surgical follow up

One hundred and eleven patients underwent open-heart surgery in Italy at the Polyclinico San Donato, while 12 patients were operated on at St Elizabeth Catholic General Hospital during organised cardio-surgical missions. One hundred and fifty-eight patients were left on the surgical waiting list for the next surgeries. Four per cent of the patients were lost during follow up and three post-surgical patients died suddenly. In addition, 25 patients died while still on the waiting list.

Discussion

This study shows that over a period of six years, 2 123 patients were seen at the St Elizabeth Catholic General Hospital cardiac centre and that congenital heart diseases were the most prevalent diagnosed pathologies, found in 13.1% ($n = 279$) of the patients. This observation is in line with previously published studies.

Transthoracic echocardiography data from the retrospective study of Mahmoud *et al*. conducted in two of Kano's laboratories in Nigeria over a period of 48 months showed that 9.3% ($n = 122$) of the patients (aged 9 days to 35 years old) presenting abnormal echocardiograms had congenital heart diseases.[7] However, another study by Bassili *et al.* conducted in Egypt showed a low incidence (1.01/1 000) of congenital heart diseases among school children.[8]

Because of its state-of-the-art facility, the Shisong Cardiac Centre, which is relatively new, is a renowned referral centre in the region. Consequently, many patients have been referred by practitioners in various disciplines, including cardiologists, paediatricians and general practitioners from different parts of the country, for better management of heart murmurs, confirmation of suspected diagnosis of congenital heart diseases and/or enrolment in the sanitary evacuation programme. This could explain the difference between our results and those of the Egyptian study.

We found that the most encountered congenital pathologies were isolated ventricular septal defect and tetralogy of Fallot. Both pathologies were also most frequently found by Bannerman and el Haq among patients with congenital heart diseases.[9,10] In addition, Ejim and colleagues showed that isolated ventricular septal defect was the most prevalent pathological condition, being diagnosed in 70% of all the cases of congenital heart diseases.[11] Acyanotic congenital heart diseases were more prevalent than cyanotic heart diseases. Cushion defects were mostly diagnosed in patients with trisomy 21.

The majority of these patients could not afford treatment due to the high cost and, as evidence of the difficulty in accessing healthcare, numerous late presentations to practitioners were registered. In a previous study by Ariane *et al*., late presentation to practitioners was observed in 79.3% of cases.[12] Both access to healthcare and the high cost of treatment also explain the very high incidence of late presentations (68.2%) recorded in Bannerman's study in Zimbabwe.[9]

We diagnosed a peri-membranous ventricular septal defect and a tetralogy of Fallot in a 13- and 16-year-old boy and girl, respectively. Adults with natural evolutive congenital heart diseases were found in 1.5% of cases.

In the sub-Saharan region of Africa, St Elizabeth Catholic General Hospital has registered the highest percentage (41%, $n = 114$) of cardiac surgeries realised abroad. Previous studies from Senegal,[13] Sudan,[14] Mauritania,[15] and Tunisia[16] have reported respectively, that only 17.3% ($n = 75$), 28% ($n = 435$), 26% ($n = 61$), and 22.5% ($n = 12$) of the patients who needed a cardiac surgical intervention actually had one done. Updated data from these countries could help clarify the state of the situation to date.

Although the cardiac centre of St Elizabeth Catholic General Hospital is relatively new, it has been the point of attraction for a growing number of new patients from neighbouring countries. Cameroon is a bilingual nation characterised by a French- and English-speaking region. However, despite the cardiac centre being located in the English-speaking region, more than 60% of the consulting patients come from the French-speaking region.

In a country with over 260 tribes, all patients are seen irrespective of their tribe and/or religious beliefs. In that respect, the hospital is a crossroads of several tribes. It might seem taboo,

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 Banso 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.

The authors thank the St Elizabeth Catholic General Hospital, Policlinico San Donato in Milan, Tertiary Sisters of St Francis, Associazione Bambini Cardiopatici nel Mondo and Cuore Fratello for providing the necessary financial support for patients' sanitary evacuation and medical treatment. Their partnership in the construction of the first paediatric cardiac surgery centre in the central and western region of Africa is also very much appreciated.

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Efficacy of intramuscular methyl prednisolone in preventing restenosis after coronary artery stenting with bare-metal stainless steel stent: a double-blind, randomised, controlled clinical trial

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Abstract

The aim of this study was to compare the mid-term outcome of patients receiving intramuscular methyl prednisolone before and after the procedure of coronary artery stenting. The study was conducted during 2007 and 2008 and compared the two arms of the study for the rate of restenosis six months after stenting. The control arm (100 patients) received only the usual preventive measures but the glucocorticoid arm (100 patients) received two doses of intramuscular methyl prednisolone (40 mg) at two-week intervals, the first at the time of the procedure. They also received the usual preventive measures

There was no statistically significant difference between the two arms for the rate of restenosis. When separately analysing for three vessels and for gender, there was no statistically significant difference either.

Lowering the dose of corticosteroid would greatly reduce the efficacy for preventing restenosis after coronary artery stenting. Therefore, if we are to achieve acceptable effectiveness with intramuscular prednisolone, we should administer increased doses at shorter intervals, which could be the target of further studies. However, there would be more chance of side effects with increased frequency of dosing.

Keywords: percutaneous transluminal coronary angioplasty stenting, restenosis, prednisolone

Submitted 14/12/09, accepted 29/3/10

Cardiovasc J Afr 2011; **22**: 67–69 www.cvja.co.za

DOI: CVJ-21.022

Although percutaneous transluminal coronary angioplasty stenting has greatly improved the outcome of patients with coronary artery disease,[1–3] there have been reports of restenosis in as many as half the cases.[4,5] Many prophylactic pharmacological interventions have been proposed to prevent restenosis after coronary artery stenting.[6–8] Previous experimental and human studies have shown that inflammation plays a key role in the process of restenosis,[9–12] and as glucocorticoids are one of the best known anti-inflammatory agents, theoretically, glucocorticoids should have beneficial preventive effects. Platelet function, smooth muscle cell proliferation and collagen synthesis as well as inflammatory cell migration and activation are some of the steps that are involved in the process of restenosis and are also targets of glucocrticoid action.[13–17] Many studies have been conducted to evaluate the clinical efficacy of this treatment modality for avoiding restenosis, with variable and sometimes even opposing results.[18-23]

Weighing up the controversial results of these studies, it seems that the route of administration, dosage and duration of glucocrticoid therapy can affect the results achieved.[24,25] There are three main routes for systemic administration of glucocorticoids; intravenous, intramuscular and the oral route. As the intramuscular route of administration is more convenient and with fewer complications than the intravenous route, and it does not have the problems of non-compliance that the oral route does, we conducted this double-blind, randomised, controlled trial to compare mid-term outcome of patients receiving intramuscular methyl prednisolone before and after the procedure of stenting with patients receiving only the usual preventive measures.

Methods

This double-blind, randomised clinical trial was conducted during 2007 and 2008 in the Shahid Madani Heart Centre of Lorestan in Iran. Patients who were admitted to hospital for percutaneous coronary intervention with bare-metal stainless steel stents were enrolled in the study. Exclusion criteria were age below 40 years and having diabetes mellitus.

Two hundred patients were selected consecutively and were randomly assigned to two groups. The groups were matched with regard to age, gender and modifiable risk factors such as smoking, family history, hyperlipidaemia and hypertension. Forty-eight hours before angioplasty, one group of patients (glucocorticoid arm) received one dose (40 mg) of intramuscular methyl prednisolone. The other group (control arm) received nothing except the usual management, which the glucocorticoid arm also received.

Thereafter, all patients were admitted to the critical care unit (CCU). They were all well hydrated, had a chest X-ray, and underwent routine laboratory studies and a diagnostic angiographic study before the procedure of percutaneous coronary angioplasty. In our centre we use clopidogrel for 45 days prior to the procedure. Finally, percutaneous coronary angioplasty with stenting was performed on both groups. Patients were discharged 24 hours after the procedure. Fourteen days later, the patients

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TABLE 1. CHARACTERISTICS AND RATE OF RESTENOSIS IN THE TWO ARMS

Arm	*n*	*Age (mean ± SD)*	*Female* n *(%)*	*Male* n *(%)*	*Restenosis* n *(%)*	*Without restenosis* n *(%)*
Glucocorticoid	100	60.29 ± 7.28	42 (42)	58 (58)	21 (21)	79 (79)
Control	100	60.44 ± 7.29	46 (46)	54 (54)	24 (24)	79 (79)

TABLE 2. CHARACTERISTICS OF THE TWO ARMS FOR EACH GENDER

Arm	*Gender*	*Total* n *(%)*	*Without restenosis* n *(%)*	*With restenosis* n *(%)*	p-*value*
Glucocorticoid	Male	54 (100)	40 (74.1)	14 (25.9)	0.831
Control		58 (100)	44 (75.9)	14 (24.1)	
Total		112 (100)	84 (75)	28 (25)	
Glucocorticoid	Female	46 (100)	39 (84.8)	7 (15.2)	0.419
Control		42 (100)	32 (76.2)	10 (23.8)	
Total		88 (100)	71 (80.7)	17 (19.3)	

in the glucocorticoid arm returned to our hospital to receive a second intramuscular dose (40 mg) of methyl prednisolone. Follow-up angiography was done six months after stenting.

Endpoints in our study were myocardial infarction, SCD, unstable angina, a positive stress echocardiographic test and observation of stenosis in the follow-up angiography. These endpoints meant that restenosis had occurred. All steps, that is, patient selection and randomisation, the initial studies, the first and second angiography, angioplasty and injections were blinded and only the head nurse of the CCU knew the patients.

Numerical variables are presented as means ± SD and categorised variables are summarised as absolute frequencies and percentages. Categorical variables were compared using the chi-square test or Fisher's exact test if required. For statistical analysis, the statistical software SPSS version 13.0 for windows (SPSS Inc., Chicago, IL) was used. All *p*-values were two-tailed, and statistical significance was defined as $p \leq 0.05$.

Results

In this double-blinded, randomised clinical trial, 200 patients were included and they were divided into two groups of the same size. The mean diameter and length of stents was 2.7 mm and 19 mm, respectively. The patients were matched regarding age, gender and four modifiable risk factors: hypertension, hyperlipidaemia, smoking and family history. Characteristics of the two groups regarding age and gender are shown in Table 1.

Twenty-one cases of restenosis were observed in the glucocorticoid arm of the study and 24 in the control arm. Restenosis was estimated with QCA. There was no statistically significant difference between the two arms in the rate of restenosis. With regard to the two genders and three vessels involved, we could not find any statistically significant difference between the two arms (Tables 2, 3).

Discussion

Our results did not show a preventive role of intramuscular methyl prednisolone in decreasing the rate of restenosis after percutaneous stenting of coronary arteries. Also, there was no significant statistical difference in the subgroups of gender and vessel involved.

TABLE 3. CHARACTERISTICS OF THE TWO ARMS FOR DIFFERENT VESSELS

Arm	*Vessel*	*Total* n *(%)*	*Without stenosis* n *(%)*	*With stenosis* n *(%)*	p-*value*
Glucocorticoid	Left anterior descending	40 (100)	31 (77.5)	9 (22.5)	0.99
Control		50 (100)	38 (76)	12 (24)	
Glucocorticoid	Left circumflex	27 (100)	21 (77.8)	6 (23.1)	0.99
Control		27 (100)	21 (77.8)	6 (22.2)	
Glucocorticoid	Right coronary artery	23 (100)	17 (73.9)	6 (17.6)	0.517
Control		23 (100)	17 (73.9)	6 (26.1)	

Despite the controversial results of previous studies regarding the efficacy of glucocorticoids in preventing restenosis, there is a widely accepted protocol that has been proved to be effective in most clinical trials performed with glucocorticoids.[18–22] To understand the lack of efficacy of our protocol, one should compare the time–action profile of our study with this accepted protocol, which includes administration of oral prednisone for a total of 45 days in different doses: 1 mg/kg for the first 10 days, 0.5 mg/kg for the next 20 days and 0.25 mg/kg for the last 15 days, starting on the day of the procedure or the following day.

By comparison, our protocol includes administration of two intramuscular doses of 40 mg of methyl prednisolone; the first dose 24 hours before the procedure and the second 14 days afterwards. Oral prednisolone exerts its effect in one to two days and intramuscular methyl prednisolone exerts its effect in one to four weeks. As the potency of the drugs is equal and their bioavailability is almost equal, using our protocol, an 80-kg patient is exposed to 1/45 the amount given to the patients in the reported protocol.[26]

Conclusion

As previous studies have shown,[25] lowering the dose of corticosteroids from this accepted protocol to even half the dose shows no efficacy in preventing restenosis after stenting, So if we are to achieve acceptable effectiveness for intramuscular prednisone, we should increase the doses using shorter intervals, which could be the target of further studies. However, there would be more chance of side effects with more frequent doses.

The authors thank the Farzan Institute for Research and Technology for technical assistance.

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Cardiovascular and electrocardiographic changes in Nigerians with a normal pregnancy

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Summary

Introduction: **Pregnancy is associated with major haemodynamic and cardiac changes, which can mimic or precipitate cardiac diseases. There is a paucity of this kind of data among pregnant Nigerian women. This study was aimed at describing the cardiovascular and electrocardiographic changes found among healthy pregnant Nigerian women.**

Methods: **This was an age-matched control study of 69 consecutive normal pregnant and 70 healthy non-pregnant controls. The study protocol included history, physical examination and 12-lead electrocardiography.**

Results: **Diastolic blood pressure < 60 mmHg was significantly commoner among pregnant subjects than controls (64.7 vs 24.3%, respectively, $p < 0.005$). Mean heart rate was higher among pregnant women (88.34 ± 11.46 bpm) than the controls (75.16 ± 12.22 bpm, $p = 0.020$). Pregnant subjects also had a higher proportion of left ventricular hypertrophy (LVH) (10.2 vs 0%, $p < 0.05$) than non-pregnant controls. Abnormal cardiac findings included a loud second heart sound (P_2), missed beats and systolic murmurs (41.2% in pregnant subjects vs 12.9% in non-pregnant controls, $p < 0.05$). Negroid-pattern ST-segment elevation was commoner among controls (24.3%) than pregnant subjects (2.9%, $p < 0.005$). Arrhythmias were rare among the study participants.**

Conclusion: **Significant findings on examination were low diastolic blood pressure and a systolic ejection murmur. However, ECG changes showed a normal frontal-plane QRS axis, normal PR interval, significantly rare normal Negroid-pattern ST elevation, significant LVH based on Araoye RI > 12 mm and a rarity of all forms of arrhythmias. These data may help resolve some cardiac diagnostic difficulties during pregnancy.**

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Keywords: cardiovascular, electrocardiographic changes, normal pregnancy, Nigeria

Submitted 1/3/10, accepted 22/4/10

Cardiovasc J Afr 2010; **21**: 71–75 www.cvja.co.za

DOI: CVJ-21.028

Pregnancy is a normal physiological phenomenon causing major haemodynamic changes, including an increase in cardiac output, as well as sodium and water retention.[1,2] In addition, these haemodynamic changes can mimic and/or precipitate cardiac diseases and cause diagnostic difficulties during pregnancy.

There is a paucity of data relating to cardiovascular (CV) and electrocardiographic (ECG) changes in healthy pregnant women in Nigeria, although the CV effects of pregnancy and associated ECG changes have been well documented outside Nigeria and Africa. Some of the notable ones are symptoms of exercise intolerance/left-sided heart failure, palpitations and syncope.[2,3] Associated physical findings that have been reported include peripheral oedema and distended neck veins.[2]

Auscultatory examinations at different stages of pregnancy may reveal a loud first heart sound (S_1) with exaggerated splitting, which may be mistaken for a fourth heart sound (S_4) or systolic click;[2] and a loud second heart sound (S_2) with persistent splitting that may simulate a loud P_2.[2] The volume-overloaded state and the augmented blood flow may produce a physiological third heart sound (S_3) and an ejection systolic murmur, respectively.[3]

ECG findings that have been reported include the QRS axis, which could be normal,[2] right or left axis;[2,4] frequent sinus tachycardia with accompanying shortened PR and QT intervals,[4] as well as higher incidence of arrhythmias.[2] Also reported are small Q waves and inverted P waves in lead III (abolished by inspiration), increased R/S ratio in leads V_1 and V_2, as well as sagging of ST segments and inversion of or flat T waves in lead III.[5]

This study was therefore undertaken to describe the CV and ECG changes in normal pregnancy among Nigerian women attending Ladoke Akintola University of Technology Teaching Hospital, Osogbo, south-west Nigeria.

Methods

This was a cross-sectional, age-matched control study of 139 patients, comprising 69 consecutive healthy pregnant and 70 healthy non-pregnant patients at Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Osun state, south-west, Nigeria. The study was carried out over a two-year period from February 2006 to January 2008. Institutional ethical clearance was obtained and all subjects gave informed consent.

All the patients were taken through a comprehensive study protocol of history and physical examination by two cardiologists. A 12-lead resting ECG with a long rhythm strip of lead

II was recorded in all subjects. The same cardiologists independently reported each ECG.

Exclusion criteria included previous or current hypertension, diabetes mellitus, thyrotoxicosis, history suggestive of congenital or valvular heart disease, or any other form of cardiac disease, sickle cell disease and anaemia (PCV < 30%) at the time of recruitment.

Araoye[6] and Sokolow-Lyon[7] criteria were independently used to assess for left ventricular hypertrophy (LVH):

Araoye criteria: R in lead I (RI) > 12 mm, or

$SV_2 + RV_6 \geq 35$ mm,

with or without T-wave inversion/flattening in V_5, V_6.

Sokolow-Lyon criteria: $SV_1 + RV_5$ (or RV_6) ≥ 35 mm with or without T-wave inversion/flattening in V_5, V_6.

Corrected QT (QTc) was calculated for each patient using Bazett's formula;[8] a normal value in females is 0.37–0.44; > 0.44 is prolonged.[9]

In cases of incomplete data, an allowance was made for 10% fall-out from the analysis. Data were compared between the two groups. Data entry was into standard forms and statistical analysis was performed. All the tests were two-sided with a 0.05 significance level set. Differences in age, parity and estimated gestational age (EGA) were by *t*-test, with chi-square for other parameters, using the Statistical Package for Social Sciences (SPSS) Chic Ill. version 11. Relative risk (RR) and 95% confidence interval (CI) were calculated using the method described by Newcombe-Wilson.[10]

Results

The age distribution in the two groups (pregnant and non-pregnant controls) was similar, with most women in the age group 20–35 years (91.3 vs 85.7%, respectively), as shown in Table 1. However, most of the patients in the control group were nulliparous (48/70, 68.6%), while parity in the pregnant group ranged between one and three offspring (41/69, 59.4%) (Table 1). There were 33, 28 and eight pregnant women in the expected gestational age groups of < 28 weeks, 28–36 weeks and > 36 weeks, respectively. Table 2 shows the summary of clinical and ECG parameters in the two groups with the relative risk, confidence intervals and *p*-values.

Diastolic blood pressure (DBP) of less than 60 mmHg was found in 64.7% of the pregnant group, versus 24.3% of the control group (RR = 2.685, CI = 1.716–4.204, $p < 0.005$). When the patients were grouped according to age, statistical signifi-

TABLE 1. AGE AND PARITY GROUP DISTRIBUTION

		Pregnant (n = *69)*	*Non-pregnant* (n = *70)*
Age (years)	< 20	1	2
	20–35	63	60
	> 35	5	8
Parity	0	23	48
	1–3	41	16
	> 3	5	6

TABLE 2. SUMMARY OF CLINICAL AND ECG FINDINGS

	Pregnant (n = *69)*	*Non-pregnant* (n = *70)*	*RR (95% CI)*	p-*value*
Mean pulse rate	84 ± 11.05	75.27 ± 8.51	–8.73 (–12.04– –5.42)	0.043
DBP < 60 mmHg	64.7% (45)	24.3% (17)	2.685 (1.716–4.204)	< 0.005
SBP (90–120 mmHg)	80.9% (56)	78.6% (55)	1.033 (0.874–1.221)	0.704
Cardiac findings	41.2% (29)	12.9% (9)	3.156 (1.610–6.189)	< 0.0005
Mean ECG heart rate	88.34 ± 11.46	75.16 ± 12.22	–13.18 (–17.15– –9.21)	0.0215
Sinus tachycardia	8.7% (6)	2.9% (2)	3.044 (0.636–14.562)	0.266
Sinus bradycardia	0	5.7% (4)	–	0.132
PR < 0.12 s	0	1.4% (1)	–	–
PR > 0.20 s	1.5% (1)	2.9% (2)	0.507 (0.047–5.466)	0.999
QRS > 0.12 s	0	1.4%	–	–
Normal QRS axis	100%	100%	–	–
LVH (RI > 12 mm)	10.2% (7)	0	0.087 (0.019–0.155)	0.0189
All LVH criteria	18.8% (13)	7.1% (5)	2.638 (0.994–7.002)	0.0399
RVH	0	0	–	0
Rsr′ (mostly lead III)	5.8% (4)	14.3% (10)	0.406 (0.134–1.232)	0.0964
Rsr′ in avF	20.3% (14)	5.1% (4)	3.551 (1.230–10.252)	0.0105
ST segment – isoelectric line (J junction on isoelectric line)	97.1% (67)	75.7% (53)	1.283 (1.116–1.473)	< 0.0005
Mild ST elevation, (Negroid-pattern ST segment)	2.9% (2)	24.3% (17)	0.119 (0.029–0.497)	< 0.0005
T-wave inversion – lead III ± any other lead	23.2% (16)	10.0% (7)	2.319 (1.018–5.284)	0.0364
Tall and broad T waves in V_2– V_6	5.8% (4)	18.6% (13)	0.312 (0.107–0.910)	0.0215
APCS	4.3% (3)	2.9% (2)	1.522 (0.262–8.828)	0.987
VPCS	2.9% (2)	2.9% (2)	–	0.622
Path Q waves	0	0	–	–
APCS and VPCS together	7.3% (5)	5.8% (4)	1.268 (0.355–4.525)	0.982
Prolonged QTc	4.3% (3)	8.6% (6)	0.493, (–0.550–1.583)	0.505

Percentage of distribution (absolute number of patients). RR = relative risk, CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy; APCS = atrial premature contractions; VPCS = ventricular premature contractions.

cance (for DBP < 60 mmHg) was reached for the age group 20–35 years ($p < 0.005$). Parity however did not affect DBP. Systolic blood pressure (SBP) was normal in both groups, ranging between 90 and 120 mmHg without any significant difference between the two groups.

On physical examination, findings ranging from grades 1–3 tricuspid systolic murmurs to loud P_2 sounds were found in 41.2% of the pregnant group, whereas only grade 1 apical systolic murmur and occasional missed beats were found in 12.9% of the control group (RR = 3.156, CI = 1.610–6.189, $p = 0.0005$). Expected gestational age did not affect clinical findings ($p = 0.738$), even when EGA grouping based on trimester was used ($p = 0.391$) (Table 3).

All patients in both groups were in sinus rhythm. Sinus arrhythmia was found only in two non-pregnant patients. Mean ECG heart rate in the pregnant and control groups were 88.34 ± 11.46 and 75.16 ± 12.22 bpm, respectively. Sinus tachycardia was rare in both groups (8.7% in pregnant vs 2.9% in controls). However, the increase in ECG heart rate in the pregnant group compared with the controls was significant (RR = –13.18, CI = –17.15 to –9.21, $p = 0.020$). The mean ECG heart rate and pulse rate were higher among the pregnant subjects than controls (88.34 ± 11.46; 84.03 ± 11.05 vs 75.16 ± 12.22; 75.27 ± 8.51 bpm, $p < 0.05$ respectively).

The frontal-plane QRS axis was normal in all pregnant patients and non-pregnant controls. LVH using Sokolow-Lyon criteria revealed no significant difference in prevalence between the two groups; however using Araoye's criterion in blacks (RI > 12 mm), the pregnant subjects had a higher prevalence of LVH than the normal controls (0.087, CI = 0.019–0.155, $p = 0.0189$). The LVH regressed in one of the two patients who reported for follow up eight weeks post partum; the other five patients were lost to follow up.

Non-specific intraventricular conduction defect was found in 5.8% of the pregnant group in the form of Rsr′, mostly in lead III, against 14.3% in the control group. Similarly Rsr′ was found in lead avF in 20.3% of the pregnant group, against 5.1% of the control (RR = 3.551, CI = 1.230–10.252, $p = 0.0105$).

Isolated atrial and ventricular ectopics were found in 7.3% of the pregnant group and 5.8% of the controls. First-degree atrioventricular block (PR > 0.20 s) was rare in both the pregnant and control groups (1.5 vs 2.9%, respectively). No other form of arrhythmia was found in either group.

Mild ST-segment elevation (J junction of the ST segment arising from within 1 mm of the isoelectric line, otherwise known as one of the 'normal variants' or the 'normal Negroid pattern' in blacks[11]) was found in 2.9% of the pregnant patients, against 24.3% in the control group (RR = 0.119, CI = 0.029–0.497, $p < 0.0005$). Isoelectric ST segment was also commoner in the pregnant subjects than the controls (97.1 vs 75.7%, RR = 1.283, CI = 1.116–0.473, $p < 0.0005$). Incidence was however less in the patients in the parity group above three (60%) when compared

TABLE 3. DISTRIBUTION OF SIGNIFICANT FACTORS IN PREGNANT GROUP ACCORDING TO TRIMESTER OF PREGNANCY

	3rd trimester		2nd trimester		1st trimester		*p*-value (Yates' chi-square)
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
Mean pulse rate	7	1	26	2	31	2	0.942 (0.119)
Mean ECG heart rate	7	1	25	3	31	2	0.945 (0.114)
Diastolic blood pressure	4	4	19	9	21	12	0.866 (0.287)
Cardiac findings	4	4	18	10	17	16	0.752 (0.571)
LVH (RI > 12 mm)	8	0	25	3	29	4	0.911 (0.186)
All LVH criteria	8	0	22	6	28	5	0.651 (0.86)
Rsr′ in aVF	3	0	19	9	28	5	0.417 (1.75)
ST-segment isoelectric line	8	0	28	0	28	5	0.196 (3.259)
Mild ST elevation (Negroid pattern)	8	0	26	2	33	0	0.564 (1.15)
T-wave inversion – lead III	8	0	21	7	24	9	0.494 (1.41)
Tall and broad T waves in V_2–V_6	8	0	26	2	32	1	0.932 (0.14)

TABLE 4. DISTRIBUTION OF SIGNIFICANT FACTORS IN PREGNANT GROUP ACCORDING TO PARITY STATUS

	0 parous		1–3 parous		> 3 parous		*p*-value (Yates' chi-square)
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
Mean pulse rate	21	2	39	2	4	1	0.925 (0.155)
Mean ECG heart rate	21	2	38	3	3	2	0.317 (2.292)
Diastolic blood pressure	16	7	27	14	3	2	0.984 (0.033)
Cardiac findings	13	10	22	19	3	2	0.971 (0.058)
LVH (RI > 12 mm)	21	2	36	5	5	0	0.978 (0.044)
All LVH criteria	20	3	33	8	5	0	0.856 (0.31)
Rsr′ in aVF	18	5	32	9	5	0	0.843 (0.34)
ST-segment isoelectric line	23	0	41	0	3	2	< 0.005 (13.50)
Mild ST elevation (Negroid pattern)	23	0	39	2	5	0	0.599 (1.023)
T-wave inversion – lead III	18	5	30	11	5	0	0.730 (0.63)
Tall and broad T waves in V_2–V_6	21	2	39	2	5	0	0.909 (0.191)

with 100% occurrence in the other parity groups: parity 0 and parity one to three ($p < 0.005$) (Table 4).

T-wave inversion in lead III ± any other lead was commoner in the pregnant group than the controls (23.2 vs 10%, RR = 2.319, CI = 1.018–5.284, $p = 0.0364$). By contrast, tall and broad T waves in V_2–V_6 occurred more commonly in the control group than the pregnant group (18.6 vs 5.8%, RR = 0.312, CI = 0.107–0.910, $p = 0.0215$).

The QTc was prolonged in a minor proportion of both the pregnant and control groups (4.3 vs 8.6%). The prolongation was however in the range of 0.46–0.47 s.

Discussion

This study showed that pregnancy in Nigerian women might be associated with cardiac and electrocardiographic changes, including low DBP, systolic ejection murmur, higher heart rate, normal frontal-plane QRS axis, rarity of Negroid-pattern ST elevation and significant LVH based on Araoye's criterion among blacks.

The low DBP was expected, because pregnancy reduces systemic vascular resistance and afterload, as a result of peripheral vasodilatation and the low resistance, high flow circulation of the uterus and placenta.[3] In this study, significantly lower DBP was nearly three times more common in the pregnant patients than in the controls, and this was supported by other studies.[2,3] Furthermore, by eight weeks' gestation, the systemic vascular resistance fell by 70% of its preconception value.[12]

The common clinical findings in this study were tricuspid systolic murmur ranging from grade 1–3 and loud P_2. The significant cardiac findings were still observed in the pregnant group, even after controlling for the possible effect of the estimated gestational age. These clinical findings were observed because the majority of the pregnancy-induced changes, such as reduced systemic vascular resistance, increased cardiac output, increased stroke volume and reduced arterial pressure occur during the first eight weeks of gestation.[12]

The ECG heart rate reached statistical significance between the two groups. Pregnancy has been well known to cause an increase in heart rate but not to the level of tachycardia. Only 8.7% of the pregnant patients had sinus tachycardia, against 2.9% of the control group. This was supported by previous studies, which reported that pregnancy only marginally increased heart rate by about 10–20 beats/min.[1-3]

The frontal-plane QRS axis was normal in all pregnant subjects, as previously reported.[13] Axis deviation was not found in any of the study participants. Other studies have reported left and right axis deviation associated with normal pregnancy.[3,5,13] We suggest that population-specific differences may account for this variation.

The incidence of atrial and ventricular premature complexes during pregnancy is unknown.[13] The low incidence in this study compared with what was obtained in normal non-pregnant subjects, as it is not unusual to find these occasional ectopics in normal non-pregnant subjects.[9]

The rarity of the 'normal Negroid-pattern' ST elevation in the study subjects might mean that the expected pregnancy-associated ST segment sagging, as previously reported in some studies,[5] depressed the ST segment to the isoelectric line. T-wave inversion in lead III ± any other lead was about twice as common in the pregnant group as in the controls. This has been reported in previous studies and is attributable to outward and upward shift of the cardiac apex by the enlarging uterus.[5]

In this study, no case of atrial fibrillation or flutter, other supraventricular tachyarrhythmias (SVT) or ventricular tachycardia was found. These conditions are rare in normal pregnancies and their presence should raise the suspicion of underlying severe cardiac disease during pregnancy.[13]

Non-specific intraventricular conduction defect (in avF) was found more frequently in the pregnant group (3.551, CI = 1.230–10.252, $p = 0.0105$). Similarly, tall and broad T waves in V_2–V_6 were found less commonly in the pregnant group than in the control group (0.312, 0.107–0.910, $p = 0.0215$). These had not been previously reported. We suggest the possibility of population-specific, pregnancy-related ECG changes. Further studies are needed to clarify this.

LVH determined from Araoye's criterion was higher in prevalence among the pregnant subjects, based on identification with increased voltage in the R wave of lead 1 > 12 mm (0.087, CI = 0.019–0.155, $p < 0.05$). This was in support of previous studies, which had demonstrated that the heart is enlarged by both chamber dilatation and hypertrophy as a result of the haemodynamic changes that occur in pregnancy.[5] Acute physiological LVH can occur rapidly during a normal human pregnancy, as an adaptive response to increased preload and cardiac work.[14] This can be demonstrated during the second trimester and is most marked at the end of pregnancy.[15] Even in a first pregnancy, the cardiovascular adaptation (LVH inclusive) begins early, can persist postpartum and appears to be enhanced by a subsequent pregnancy.[16]

The follow up of the patients eight weeks postpartum with a repeat ECG revealed normal voltage in the ECG in one out of two subjects who reported back for follow up. Reversal of chamber and hypertrophic changes of normal pregnancy has been shown to occur from a variable period of eight weeks to more than one year post delivery, due to the reversal of the haemodynamic changes associated with pregnancy.[14-18] However, the proportion of subjects who reported back was too small to draw a meaningful conclusion on this and further studies are therefore suggested.

In Table 4, multiparity (> three) showed statistical significance in only the ST-segment isoelectric line parameter ($p < 0.005$), where three out of five in the more-than-three parity group were affected. The volume-overloaded state (with increased preload) of pregnancy causes physiological LVH;[17] after the first pregnancy, subsequent pregnancies have been shown to enhance this.[16] Similarly, as mentioned, the expected pregnancy-associated ST-segment sagging depressed the 'Negroid pattern' ST-segment elevation to the isoelectric line. LVH is responsible for the ST segment sagging, hence the parity-related enhancement of the physiological LVH would account for more multiparous women having their ST segment on the isoelectric line.

However, findings from our study were not in conformity with above arguments, as fewer patients in grand multiparous groups had demonstrable ST isoelectric lines. Echocardiographic indices could elucidate more correctly these haemodynamic changes and clarify this grey area.

The major limitation in this study was the small sample size and this is evident in the wide range demonstrated in the various confidence intervals.

Conclusion

This study has provided data on the common cardiovascular and ECG findings in healthy pregnant women in Nigeria. The most common findings on physical examination were low diastolic blood pressure and systolic ejection murmur. There were also some distinctive ECG features, which may help to differentiate cardiac disease in pregnancy from normal cardiac findings in our practice area. In the pregnant Nigerian woman, normal frontal-plane QRS axis, normal PR interval and ST segment arising from the isoelectric line are more or less the rule. LVH based on Araoye RI > 12 mm could be seen in a few others, while all forms of arrhythmia were rare.

The authors express their gratitude to all patients for their consent and cooperation. We thank all the residents in the Departments of Medicine and Obstetrics and Gynaecology for their contributions to the successful completion of the study. We are also grateful to the two ECG technicians in the cardiology unit of the hospital, Mrs Oyekale and Mrs Iyiola, as well as Mrs Bose Olaniyan, the chief nursing officer, for their invaluable contributions. We acknowledge the role of Mr Adeola Ayileka and Mr Peter Awosanmi of the Malaria Research Unit in the study. Finally, we are grateful to Mr Bonaventure Makinde of the Department of Radiology, College of Health Sciences, Lautech for regular secretarial assistance.

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Diary for 2011 cardiovascular congresses

DATE	PLACE	CONFERENCE	WEBSITE
4–5 May	Tel Aviv, Israel	58th annual conference of the Israel Heart Society in association with the Israeli Society of Cardiothoracic Surgery	www.israelheart.com
21–24 May	Gothenburg, Sweden	Heart Failure congress 2011	www.escardio.org/congresses/HF2011/
27–30 May	Kampala, Uganda	10th Pan-African Society of Cardiology (PASCAR) congress	www.pascar.co.za
22 June	Frankfurt, Germany	Imaging in Cardiovascular Interventions (ICI)	www.ici-congress.org/
27–31 August	Paris, France	European Society of Cardiology congress (ESC)	www.escardio.org/congresses/esc-2011/
29 September – 1 October	Sri Lanka	Asia Pacific Stroke conference	www.apsc2011.com
23–26 October	International Convention Centre, East London, South Africa	SA Heart congress	www.saheart.co.za
12–16 November	Orlando, Florida, USA	American Heart Association (AHA)	www.americanheart.org

P-wave dispersion: relationship to left ventricular function in sickle cell anaemia

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Summary

***Background*: The prognostic implications of P-wave dispersion in patients with a variety of cardiac disease conditions are increasingly being recognised. The relationship between P-wave dispersion and left ventricular function in sickle cell anaemia is unknown.**

***Objective:* This study was aimed at evaluating the relationship between P-wave dispersion and left ventricular function in adult Nigerian sickle cell anaemia patients.**

***Methods:* Between February and August 2007, a total of 62 sickle cell anaemia patients (aged 18–44 years; mean 28.27 ± 5.58) enrolled in the study. These were drawn from patients attending the adult sickle cell clinic of the University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu. An equal number of age- and gender-matched normal subjects served as controls. All the participants were evaluated with electrocardiography and echocardiography. P-wave dispersion was defined as the difference between the maximum and minimum P-wave duration measured in a 12-lead electrocardiogram.**

***Results:* P-wave duration and P-wave dispersion were significantly higher in patients than in controls. Significant correlation was demonstrated between P-wave dispersion and age in the patients (r = 0.387; p = 0.031). A comparison of subsets of sickle cell anaemia patients and controls with comparable haematocrit values (30–35%) showed significantly higher P-wave duration and P-wave dispersion in the patients than in the controls. The P-wave duration in patients and controls, respectively, was 111.10 ± 14.53 ms and 89.14 ± 16.45 ms (t = 3.141; p = 0.006). P-wave dispersion was 64.44 ± 15.86 ms in the patients and 36.43 ± 10.35 ms in the controls (t = 2.752; p = 0.013). Significant negative correlation was found between P-wave dispersion and left ventricular transmitral E/A ratio (r = –0.289; p = 0.023).**

***Conclusion:* These findings suggest that P-wave dispersion could be useful in the evaluation of sickle cell patients with left ventricular diastolic dysfunction. Further prospective studies are recommended to evaluate its prognostic implication on the long-term disease outcome in sickle cell disease patients.**

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Keywords: P-wave dispersion, left ventricular function, sickle cell anaemia

Submitted 9/3/10, accepted 3/5/10

Cardiovasc J Afr 2010; **21**: 76–78 www.cvja.co.za

DOI: CVJ-21.031

There is increasing recognition of the prognostic implications of the spatial variations of P-wave duration in normal individuals and patients with a variety of cardiac disease states.[1-3] P-wave dispersion is defined as the deference between the maximum and minimum P-wave duration measured in a 12-lead electrocardiogram.[4] It is related to the non-homogeneous and interrupted conduction of sinus impulse both intra- and interatrially and is considered a predictor of the occurrence of arrhythmias in patients with left atrial enlargement, left ventricular hypertrophy and left ventricular diastolic dysfunction,[5] all of which are significant findings in sickle cell anaemia.[5,6] There is scant information on this subject in the literature. The study is undertaken to evaluate the relationship between P-wave dispersion and left ventricular function in adult Nigerian sickle cell anaemia patients.

Methods

A cross-sectional study was carried out on 62 sickle cell anaemia patients seen at the adult sickle cell clinic of the University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla, Enugu from February to August 2007. An equal number of age- and gender-matched normal subjects served as controls. All the participants were evaluated with electrocardiography and echocardiography.

Resting 12-lead electrocardiography was performed on all subjects using a Cardioline Ar-600 model electrocardiography machine at a paper speed of 25 mm/s and standardised at 0.1 mV/mm. A single observer analysed the electrocardiogram. The P-wave was measured from the beginning of the P-wave deflection from the isoelectric line to the end of the deflection returning to the isoelectric line. If the beginning or end of the deflection could not be satisfactorily defined, that lead was not used. The difference between the maximum and minimum P-wave duration was taken as the P-wave dispersion.[4]

Echocardiography was done using a Hewlett Packard Sonos 2500 echocardiography machine with 3.7-MHz transducer. The following measurements were taken in the standard positions as recommended by the American Society of Echocardiography:[7,8] left atrial dimension, aortic root dimension, left ventricular end-systolic dimension, left ventricular end-diastolic dimension and end-diastolic volumes, velocities of E and A waves, isovolumic relaxation time and E-wave deceleration time, left ventricular ejection fraction, fractional shortening, and velocity of circumferential shortening.

Ethical clearance for the study was obtained from the ethics committee of UNTH, Enugu. Prior informed consent was obtained from all the participants in the study.

Statistical analysis

Data were presented as means ± standard deviation. Comparison of continuous variables between the group of sickle cell disease patients and the control group was made with the independent Student's *t*-test. In order to examine the effect of anaemia on the variables, the subjects were classified, based on the haematocrit values, into four classes in accordance with the World Health Organisation classification of anaemia as follows: class 1, normal (haematocrit ≥ 36%); class 2, mild anaemia (haematocrit 30–35.9%); class 3, moderate anaemia (haematocrit 21–29.9%); class 4, severe anaemia (haematocrit 18–20.9%).[9]

Inter-class differences in clinical, electrocardiographic and echocardiographic parameters in the patients were compared by one-way analysis of variance and *post hoc* multiple comparison of means using the Tukey's honestly significant difference test. Intra-class differences in parameters between patients and controls in the same haematocrit class were analysed using the independent Student's *t*-test. The relationship between P-wave dispersion and echocardiographic indices of left ventricular function (while controlling for the effect of anaemia) (haematocrit) was examined using the partial correlation analysis.

Results

The mean ages of the patients and controls were 28.27 ± 5.58 (range 18–44) and 28.37 ± 5.91 (range 18–45) years, respectively. There were no statistically significant age and gender differences between patients and controls. The patients had statistically significant lower mean values than the controls in the measurement of height, body mass index and body surface area ($p < 0.001$, Table 1).

P-wave duration and P-wave dispersion were significantly higher in patients than controls (Table 2). Significant correlation was demonstrated between P-wave dispersion and age in the patients ($r = 0.387$; $p = 0.031$). When subsets of sickle cell anaemia patients and controls with comparable haematocrit values (30–35%) were compared, the patients were found to have significantly higher P-wave duration and dispersion than the controls. The P-wave duration in patients and controls, respectively, was 111.10 ± 14.53 ms and 89.14 ± 16.45 ms ($t = 3.141$; $p = 0.006$). P-wave dispersion was 64.44 ± 15.86 ms in the patients and 36.43 ± 10.35 ms in the controls ($t = 2.752$; $p = 0.013$).

In order to evaluate the effect of degree of anaemia on P-wave dispersion in the patients, the electrocardiographic parameters were compared among the haematocrit categories, as shown in Table 3. The haematocit values had no effect on the P-wave duration or dispersion.

The result of a multivariate Pearson's correlation analysis of P-wave dispersion and echocardiographic indices of left ventricular function are presented in Table 4. Of all the parameters evaluated, significant negative correlation was found between P-wave dispersion and left ventricular transmitral E/A ratio ($r = 0.289$; $p = 0.023$). The correlation was still significant after controlling for the effect of anaemia ($r = 0.285$; $p = 0.027$). Such correlation was not observed in the normal controls ($r = 0.025$; $p = 0.859$).

Discussion

This study revealed a significant increase in P-wave dispersion in sickle cell anaemia patients. The finding of a negative correlation between P-wave dispersion and left ventricular E/A ratio suggests that left ventricular diastolic function might be deranged in patients with increased P-wave dispersion. Reduced left ventricular relaxation and alteration in left ventricular chamber compliance are the haemodynamic abnormality for left

TABLE 1. AGE, GENDER AND ANTHROPOMETRIC DATA

Parameters	*SCA mean (SD)*	*Controls mean (SD)*	t-*test*	p-*value*
Age (years)	28.27 (5.58)	28.37 (5.91)	0.987	0.924
Gender (frequency (%))			0.00	1.00[a]
Male	31 (50)	31 (50)		
Female	31 (50)	31 (50)		
Total	62	62		
Weight (kg)	54.97 (10.61)	67.35 (8.37)	7.20	< 0.001*
Height (m)	1.62 (0.14)	1.72 (0.07)	4.960	< 0.001*
Body surface area (m^2)	1.62 (0.03)	1.78 (0.14)	3.723	< 0.001*
Body mass index (kg/m^2)	20.47 (2.73)	23.87 (3.22)	6.181	< 0.001*

*Statistically significant, [a]Chi-square, SCA = sickle cell anaemia.

TABLE 2. COMPARISON OF ELECTROCARDIOGRAPHIC CHARACTERISTICS OF PATIENTS AND CONTROLS

	Values; mean (SD)			
Variables	*SCA*	*Controls*	t-*test*	p-*value*
Heart rate (beat/min)	80.61 (12.79)	68.98 (4.24)	6.327	< 0.001*
P-wave duration (ms)	128.0 (14.15)	90.30 (14.84)	14.189	< 0.001*
P-wave dispersion (ms)	65.7 (16.09)	34.7 (17.41)	9.014	< 0.001*

*Statistically significant, SCA = sickle cell anaemia.

TABLE 3. ELECTROCARDIOGRAPHIC PARAMETERS IN SICKLE CELL ANAEMIA; EFFECT OF HAEMATOCRIT LEVELS

	Haematocrit levels; mean (SD)				
Parameters	*Mild*	*Moderate*	*Severe*	F-*statistic*	p-*value*
Heart rate (beat/min)	83.56 (12.34)	77.65 (12.85)	83.27 (11.76)	1.391	0.297
P-wave duration (ms)	111.10 (14.50)	136.50 (17.31)	109.11 (16.40)	0.228	0.797
P-wave dispersion (ms)	64.42 (12.86)	64.04 (17.10)	60.02 (15.50)	0.245	0.784

*Statistically significant.

TABLE 4. MULTIVARIATE PEARSON'S CORRELATION OF P-WAVE DISPERSION AND ECHOCARDIOGRAPHIC PARAMETERS IN PATIENTS AND CONTROLS WHILE CONTROLLING FOR HAEMATOCRIT

	Patients		*Controls*	
Variables	*Pearson's* r	p-*value*	*Pearson's* r	p-*value*
LVMI	–0.0489	0.712	–0.0538	0.680
Fractional shortening	–0.1507	0.250	–0.1988	0.124
Ejection fraction	0.0489	0.711	0.0510	0.696
VCS	0.0607	0.645	–0.0541	0.679
E/A ratio	–0.285	0.027*	0.025	0.859
IVRT	0.1659	0.205	–0.0735	0.573
EDT	–0.01049	0.425	0.0005	0.997
Cardiac index	–0.2369	0.066	–0.0825	0.531

*Statistically significant; LVM = left ventricular mass, VCS = velocity of circumferential shortening, IVRT = isovolumic relaxation time, EDT = E-wave deceleration time.

ventricular diastolic dysfunction. Left ventricular hypertrophy, cardiomyopathy, myocardial ischaemia, systemic hypertension and normal aging are recognised causes. In diastolic dysfunction, rapid early filling is decreased, pressure upstream of the left ventricle is increased and atrial systole therefore has a crucial role to play to decrease atrial pressure and resume left ventricular filling.

P-wave dispersion has been described as a non-invasive indicator of risk of atrial fibrillation.[1] If atrial fibrillation occurs, the loss of atrial systolic contribution to the left ventricular diastolic filling results in progressive diastolic dysfunction. Increased P-wave dispersion has been noted in hypertensive patients with diastolic dysfunction when compared with patients without diastolic dysfunction.[10] Although some studies have suggested that left atrial diameter is an important predictor of atrial fibrillation, and that P-wave duration is related to left atrial dimension, the present study did not observe any relationship between P-wave dispersion and left atrial dimension.[11,12]

P-wave dispersion in sickle cell anaemia positively correlated with patients' age (duration of illness), suggesting a progressive deterioration with time. Ayetemir and associates,[13] in an investigation of clinical variables that affect P-wave dispersion in normal subjects, identified age as a related variable. However, in this study, no such correlation was observed in the control subjects. The authors are not aware of any previous study on P-wave dispersion in sickle cell anaemia. In view of the fact that diastolic dysfunction is a common cardiac complication of sickle cell anaemia, this study could be considered as an initial evaluation of the usefulness of this simple, non-invasive diagnostic tool in the assessment of diastolic function in sickle cell anaemia patients.

Conclusion

P-wave dispersion was increased in patients with sickle cell anaemia and significantly correlated positively with age and negatively with left ventricular diastolic function. These findings suggest that P-wave dispersion could be useful in the evaluation of sickle cell patients with left ventricular diastolic dysfunction. However, further prospective studies are recommended to evaluate its prognostic implication on the long-term disease outcome in sickle cell disease patients.

We thank Mrs Dora Okorogu of the Cardiac Centre, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu for offering technical support in electrocardiographic recording.

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Achieving blood preSsure goals sTudy in uncontrolled hypeRtensive pAtients treated with a fixed-dose combination of ramipriL/hydrochlorothiazide: the ASTRAL study

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Abstract

Background: **Hypertension is a common cardiovascular disease, affecting adults worldwide and it accounts for up to 30% of all deaths. The need for better control of arterial hypertension justifies observational studies designed to better understand the real-life management of hypertensive patients. The ASTRAL study was primarily designed to evaluate the percentage of hypertensive patients achieving blood pressure goals after eight weeks of treatment with a fixed-dose combination of ramipril/hydrochlorothiazide (HCTZ).**

Methods: **The study was a multi-centre, non-comparative, open-label, observational study conducted in 36 centres in five sub-Saharan African countries, namely Cameroon, Congo Brazzaville, Democratic Republic of Congo (DRC), Madagascar and Nigeria. Four hundred and forty-nine men and women 18 years of age or older with hypertension not controlled by an ACE inhibitor, a diuretic or any other monotherapy or anti-hypertensive combination not containing a diuretic in a fixed dose were considered eligible for inclusion in this eight-week study. The study consisted of three visits, visit one (V1) at baseline, visit two (V2) after four weeks and visit three (V3) after eight weeks.**

Results: **The mean age of the patients was 54.7 ± 11.7 years (20–90 years) and most were categorised by the WHO criteria as either overweight or obese (71.6%). After four and eight weeks of treatment with the study drug, systolic and diastolic blood pressures significantly changed from baseline: –24.7/–14.2 mmHg ($p < 0.001$) and –31.7/–17.9 mmHg ($p < 0.001$), respectively. There were 60.2% of the non-diabetics on prior monotherapy who, at eight weeks, fulfilled the primary blood pressure goal for SBP and DBP, versus 26.5% of the diabetic patients, also on monotherapy. Few adverse events were reported, with facial oedema and dry cough recurring twice in two patients.**

Conclusion: **Fixed-dose combination of ramipril/HCTZ is therefore effective, tolerable and has a good safety profile for blood pressure control in black Africans.**

Keywords: hypertension, ramipril, black Africans, ACE inhibitors, thiazides

Submitted 3/3/10, accepted 21/9/10

Cardiovasc J Afr 2011; **22**: 79–84 www.cvja.co.za

DOI: CVJ-21.069

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Hypertension is the most prevalent cardiovascular (CV) disease in adults worldwide and is a major risk factor for both cardiovascular and cerebrovascular morbidity and mortality.[1] Systemic arterial hypertension is globally estimated to affect 30% of adults[2,3] and to account for up to 30% of all deaths.[1] Although the results of several cross-sectional and cohort epidemiological studies show that the prevalence of hypertension varies significantly,[4–9] the prevalence in sub-Saharan Africa varies between 12 and 29%, depending on the country.[10] In developed countries, fewer than 27% of patients with arterial hypertension have controlled blood pressure (BP),[3] whereas in developing countries this number is less than 10%.[11] The relationship between BP and CV risk is continuous, such that every 20-mmHg rise in systolic blood pressure (SBP) or 10-mmHg rise in diastolic blood pressure (DBP) doubles the risk of cardiovascular disease (CVD).[12] Therapy with anti-hypertensive drugs have shown a 35 to 40% reduction in stroke, a 20 to 25% reduction in myocardial infarction, a more than 50% reduction in heart failure, and reductions in CVD-related death rates.[3]

Age, ethnicity, obesity, smoking, excessive consumption of alcohol and physical inactivity are among the risk factors identified to be associated with hypertension. The JNC-7 and recent European guidelines[3,11] have recommended BP goals at the following levels: < 140/90 mmHg in non-diabetic hypertensive patients, and < 130/80 mmHg in diabetic hypertensive patients. Both the JNC-7 and the European guidelines have also recommended BP treatment with at least two agents or using a combination of diuretic and another antihypertensive agent that has a different mode of action for patients presenting with BP values

≥ 20/10 mmHg above the BP goals.[3,11] Additionally, fixed-drug combinations offer several advantages over the separate prescription of individual drugs.[11] The need for better control of arterial hypertension justifies observational studies designed to better understand the real-life management of hypertensive patients, especially in Africa, where few hypertension studies have been conducted.

The primary outcome of the ASTRAL study was to evaluate the percentage of hypertensive patients achieving BP goals after eight weeks of treatment with a fixed-dose combination of ramipril/HCTZ, hence to generate data on the effectiveness of the fixed-dose combination.

Ethics committee approval to undertake the survey was obtained from hospitals in each country in accordance with national and local regulations. Written, signed consent was obtained from each of the patients included. The study was conducted in accordance with the Helsinki II Declaration.

Methods

The study was a multi-centre, non-comparative, open-label, observational study conducted across 36 centres in five sub-Saharan African countries (Cameroon, Congo Brazzaville, DRC, Madagascar and Nigeria). Men and women 18 years of age or older with arterial hypertension uncontrolled by an ACE inhibitor, a diuretic, or any other monotherapy or anti-hypertensive combination not containing a diuretic in a fixed dose were considered eligible for inclusion in the study. Exclusion criteria were: known hypersensitivity to any component of the study drug (Tritazide®), history of angio-oedema, patients with severe renal or hepatic dysfunction, severe gout, secondary hypertension, and all pregnant or breastfeeding women. Although the study was initially planned to include 460 consecutive hypertensive patients from the 36 participating centres, only 449 patients could be recruited and included to receive the study drug; 408 (90.9%) of these patients completed the study. The reasons for non-completion of the study are summarised in Fig. 1.

Three visits were scheduled during the study. At visit one (week 0), demographic data, history of co-morbidities, duration of hypertension, blood pressures at first diagnosis of hypertension and previous anti-hypertensive treatment given, concomitant medications, and CV risk factors were recorded. SBP and DBP were measured and recorded in the seated position after five minutes of rest in the medical office, using a validated and calibrated electronic sphygmomanometer (OMRON M7, OMRON, Tokyo, Japan) with an appropriate cuff size. A blood pressure target was established, recommended lifestyle modifications were given to the patient and the ramipril/HCTZ daily dose was prescribed, based exclusively on the decision of the treating physician and in accordance with the prescribing information in the summary of the product characteristics or package insert. Body weight was recorded in kilograms and height was measured in metres to determine the body mass index (BMI) which was recorded as overweight if ≥ 25 kg/m^2 and obese if ≥ 30 kg/m^2, according to the WHO guidelines.[13]

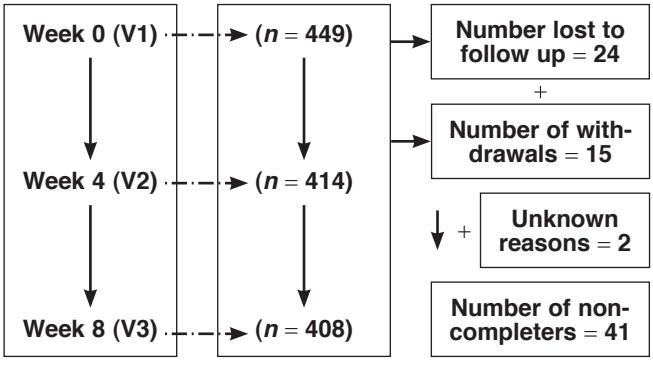

Fig. 1. Study time line and reasons for non-completion of study.

At the follow-up visits at weeks four and eight (visits two and three, respectively), BP was measured, adverse events were assessed and treatment compliance rating was evaluated by taking into account the unused number of tablets returned by the patient on the follow-up visit and expressed as good (< four of 28 tablets returned), average (five to nine of 28 tablets returned) or poor (≥ 10 of 28 tablets returned). The necessity for titration to a higher dose of the study drug was evaluated in response to BP goal.

The primary outcome of the ASTRAL study was to evaluate the percentage of hypertensive patients achieving BP goals after eight weeks of treatment with a fixed-dose combination of ramipril/HCTZ. Blood pressure control was defined as SBP < 140 mmHg and/or DBP < 90 mmHg in non-diabetics and SBP < 130 mmHg and/or DBP < 80 mmHg in diabetic patients. The secondary objectives included the assessment of variations in SBP and DBP values between visits, compliance with treatment, tolerance of the treatment and the factors influencing BP control.

Statistical analysis

The statistical analysis was performed by ClinStat CC, Pretoria, South Africa. All analyses were carried out on SAS (release 9.1.3). Descriptive statistical analyses were performed. Qualitative variables were expressed as frequency counts and percentages. Quantitative variables were summarised by mean values, standard deviations, minimum and maximum values. Within-subject comparisons (changes in blood pressures at weeks four and eight relative to baseline) were tested for significance by the paired *t*-test.

A logistic regression analysis was performed with goal achievement as a dependent variable and the following predictor variables: age, gender, history of diabetes, alcohol consumption, renal dysfunction, diabetic nephropathy, microalbuminuria, cerebrovascular accident and heart failure, BMI, concomitant treatment with NSAIDs, daily dose of study drug and BP at inclusion. In the logistic regression analysis, the following predictor variables were numeric: age, systolic blood pressure, diastolic blood pressure and daily doses of study drugs. All the other predictor variables were categorical. Adverse events were listed, indicating intensity, relationship with the study drug, discontinuation in the study, corrective treatment, outcome and seriousness. A p-value < 0.05 was considered as significant.

Results

The baseline demographic and clinical features, co-morbidities and associated CV risk factors of all the patients and for patients from the five participating countries are shown in Tables 1 and 2. Four hundred and forty-nine hypertensive patients took part in the study, with a mean age of 54.7 ± 11.7 years (range 20–90

TABLE 1. THE BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS

Characteristic	*All* (n = *449)*	*Cameroon* (n = *100)*	*Congo* (n = *87)*	*DRC* (n = *62)*	*Madagascar* (n = *100)*	*Nigeria* (n =*100)*
Age (years)	54.7 ± 11.7	55.2 ± 11.1	58.3 ± 13.1	54.0 ± 12.3	51.7 ± 10.4	54.2 ± 11.3
Male (%)	198 (44.1)	46 (46.0)	31 (35.6)	27 (43.5)	44 (44.0)	50 (50.0)
BMI (kg/m^2)	28.1 ± 5.3	29.2 ± 5.3	27.6 ± 5.3	28.6 ± 5.6	25.6 ± 3.9	29.9 ± 5.4
Alcohol users (%)	87 (19.4)	32 (32.0)	19 (21.8)	10 (16.1)	8 (8.0)	18 (18.0)
Duration of hypertension (years)	6.2 ± 6.5	4.4 ± 5.2	7.2 ± 7.8	5.9 ± 4.9	7.1 ± 5.6	6.6 ± 7.9
Number of anti-hypertensive agents in use:						
0	40 (8.9)	10 (10.0)	–	5 (8.1)	15 (15.0)	10 (10.0)
1	278 (61.9)	50 (50.0)	78 (89.7)	35 (56.4)	72 (72.0)	43 (43.0)
2	99 (22.0)	29 (29.0)	8 (9.2)	18 (29.0)	10 (10.0)	34 (34.0)
3	28 (6.2)	11 (11.0)	1 (1.1)	2 (3.2)	3 (3.0)	11 (11.0)
4	3 (0.7)	–	–	2 (3.2)	–	1 (4.0)
Not sure	1 (0.2)	–	–	–	–	1 (4.0)
SBP (mmHg)	168.9 ± 19.2	178.6 ± 19.9	180.7 ± 24.9	173.7 ± 20.7	174.2 ± 20.4	166.3 ± 22.1
DBP (mmHg)	102.6 ± 12.3	105.0 ± 12.1	103.5 ± 13.0	101.7 ± 12.3	105.0 ± 11.5	101.3 ± 13.0
No using ≤ 1 anti-hypertensive agents (%)	318 (70.8)	60 (60.0)	78 (89.7)	40 (64.5)	87 (87.0)	53 (53.0)

DRC: Democratic Republic of Congo, BMI: body mass index, SBP: systolic BP, DBP: diastolic BP. Values are given as mean ± SD or as number of cases (%).

TABLE 2. PERCENTAGES OF PATIENTS WITH CO-MORBIDITIES AND SPECIFIED CARDIOVASCULAR RISK FACTORS

Co-morbidities or CV risk factors	*All* n *(%)*	*Cameroon* n *(%)*	*Congo* n *(%)*	*DRC* n *(%)*	*Madagascar* n *(%)*	*Nigeria* n *(%)*
Patients with associated co-morbidities	160 (35.6)	32 (32.0)	29 (33.3)	50 (80.7)	14 (14.0)	35 (35.0)
Cerebrovascular accident	31 (6.9)	10 (10.0)	9 (10.3)	3 (4.8)	2 (2.0)	7 (7.0)
Coronary artery disease	6 (1.3)	–	3 (3.4)	2 (3.2)	–	1 (1.0)
Heart failure	29 (6.5)	1 (1.0)	3 (3.4)	19 (30.6)	–	6 (6.0)
Diabetic nephropathy and microalbuminuria	19 (4.2)	5 (5.0)	3 (3.4)	5 (8.0)	–	6 (6.0)
Others	75 (16.7)	16 (16.0)	11 (12.5)	21 (34.1)	12 (12.0)	14 (14.0)
Cardiovascular risk factors						
Overweight/obese	320 (71.6)	63 (63.0)	46 (52.9)	33 (53.2)	54 (54.0)	50 (50.0)
Smokers	21 (4.7)	2 (2.0)	1 (1.1)	2 (3.2)	14 (14.0)	2 (2.0)
Dyslipidaemia	72 (16.0)	9 (9.0)	13 (14.9)	13 (21.0)	24 (24.0)	13 (13.0)
Diabetes	88 (19.6)	7 (7.0)	33 (37.9)	4 (6.4)	24 (24.0)	20 (20.0)
No CV risk factor	77 (17.1)	2 (2.0)	22 (25.3)	17 (27.4)	24 (24.0)	12 (12.0)

DRC: Democratic Republic of Congo.

years) and with 11.1% of all the participants being ≤ 40 years old. The mean duration of hypertension was 6.2 ± 6.5 years and there was a slight female preponderance in the study population (male = 44.1%). The mean BMI was 28.1 ± 5.3 kg/m^2 and most of the patients were categorised as either overweight or obese (72%).

Patients with a history of diabetes made up 19.6% of the study population and 2.4% were unaware of their diabetes status. There was a high number of patients with associated hypertension-related end-organ damage or co-morbidities (35.6%), such as previous cerebrovascular accidents, coronary artery disease and heart failure, accounting for 6.9, 1.3 and 6.5%, respectively. At the start of the study, only 17.1% of the patients had no known CV risk factor. No statistically significant differences were observed between the different countries in the baseline characteristics of the patients.

At baseline, the mean SBP and DBP were 168.9 ± 19.2 and 102.6 ± 12.3 mmHg, respectively and most of the patients (70.8%) had been on only one or no anti-hypertensive agent before the study. Also, most of the patients (99.1% at V1, 91.5% at V2 and 88.7% at V3) started and remained on a standard dose (5/25 mg) or half-standard dose (2.5/12.5 mg) of the fixed-dose combination ramipril/HCTZ for the duration of the study (Table 3).

The patterns of BP changes observed in this study were similar across the five participating countries. At V2 and V3, BP significantly changed from baseline: –24.7/–31.7 for SBP mmHg ($p < 0.001$) and –14.2/–17.9 mmHg ($p < 0.001$) for DBP (Table 3). Table 4 shows the mean and changes in SBP and DBP from visit one in patients receiving monotherapy and dual or more therapy before and after commencement of the study. SBP and DBP changes were similar in patients who had been on monotherapy and those who had been on dual or more therapy. There were 60.2% of the non-diabetic patients on prior monotherapy who fulfilled the primary BP goal at V3 for SBP and DBP, versus 26.5% of diabetic patients on monotherapy. Of those patients on prior dual or more anti-hypertensive therapy, 41.5% of the non-diabetics (vs 14.3% of diabetics) met the primary BP goal at visit three (Table 5).

Compliance with the fixed-dose combination of ramipril/HCTZ was 89.2% at week four and 92.6% at week eight of the study (Table 3). In all, six patients reported eight different episodes of adverse events, with facial oedema and dry cough being reported twice by two different patients at separate times. Urinary retention, gout, repeated epistaxis and generalised body weakness were all reported once by different patients (Table 6). Adverse events occurred only in patients on half-standard or standard-dose therapy.

The multivariate logistic regression analysis showed that in the ASTRAL study, diabetes was the most significant factor independently associated with BP goal attainment. The likelihood of achieving BP control in diabetic patients was 4.94 times less than in non-diabetic patients (OR: 4.92; 95% CI: 2.57–9.64; $p < 0.05$). Other factors associated with the attainment of BP goal were age (OR: 0.98; 95% CI: 0.97–0.99; $p < 0.05$), DBP (OR: 0.98; 95% CI: 0.97–0.99; $p < 0.05$) and SBP (OR: 0.99; 95% CI: 0.96–0.99; $p < 0.05$). However, with the logistic regression performed separately for diabetics and non-diabetics, no statistically significant predictors were found for goal achievement for diabetic patients. SBP at visit one was the only significant predictor of goal achievement in non-diabetic patients (OR: 0.969; 95% CI: 0.953–0.986; $p = 0.0003$).

TABLE 3. TREATMENT SCHEDULE OF TRITAZIDE, MEAN BP CHANGES FROM BASELINE AND STUDY DRUG COMPLIANCE.

Dose of Tritazide (ramipril/HCTZ) (mg)	*Number (%) of patients*		
	Week 0 (V 1)	*Week 4 (V 2)*	*Week 8 (V 3)*
2.5/12.5	173 (38.7)	77 (18.7)	65 (16.0)
5/25	270 (60.4)	299 (72.8)	295 (72.7)
7.5/37.5	–	5 (1.2)	14 (3.4)
10/50	4 (0.9)	30 (7.3)	32 (7.9)
Blood pressures and BP changes from baseline			
SBP (mmHg)	168.9 ± 19.2	143.5 ± 19.7	136.5 ± 15.5
Δ SBP (mmHg)	NA	– 24.7*	–31.7*
DBP (mmHg)	102.6 ± 12.3	88.7 ± 11.9	84.8 ± 9.9
Δ DBP (mmHg)	NA	–14.2*	–17.9*
Study drug compliance	*n* = 449	*n* = 408	*n* = 407
Good	NA	364 (89.2)	377 (92.6)
Medium	NA	34 (8.3)	21 (5.2)
Poor	NA	10 (2.5)	9 (2.2)

HCTZ: hydrochlorothiazide, V1: visit one, V2: visit two, V3: visit three, BP: blood pressure, SBP: systolic BP, DBP: diastolic BP, Δ SBP: change in systolic BP from baseline, Δ DBP: change in diastolic BP from baseline, NA: not applicable; *$p < 0.001$.

Discussion

High blood pressure is a major risk factor for cardiovascular morbidity and mortality worldwide. In sub-Saharan Africa, hypertension is one of the greatest health challenges after HIV/AIDS.[1,14] Some key issues related to hypertension management in black Africans have been highlighted from this study: the high prevalence of hypertension-related co-morbidities; the high level of uncontrolled BP; the high prevalence of overweight and obesity among black Africans; the effectiveness of a combination of an ACE inhibitor and diuretic in controlling BP in Africans; the lower BP control achieved with an ACE inhibitor and diuretic combination in black African hypertensive patients with diabetes within the first eight weeks; and the good tolerability of the ACE

TABLE 5. BP GOAL ATTAINMENT AT VISIT THREE IN PATIENTS WHO RECEIVED MONOTHERAPY AND THOSE WHO RECEIVED DUAL OR MORE THERAPY

	Monotherapy	*Dual or more therapy*
Non-diabetics	(*n* = 186)	(*n* = 106)
(a) SBP < 140 mmHg and DBP < 90 mmHg	112 (60.2)	44 (41.5)
(b) SBP < 140 mmHg [including patients counted in (a) above]	126 (67.7)	53 (50.0)
(c) DBP < 90 mmHg [including patients counted in (a) above]	134 (72.0)	62 (58.5)
Diabetics	(*n* = 49)	(*n* = 21)
(a) SBP < 130 mmHg and DBP < 80 mmHg	13 (26.5)	3 (14.3)
(b) SBP < 130 mmHg [including patients counted in (a) above]	21 (42.9)	5 (23.8)
(c) DBP < 80 mmHg [including patients counted in (a) above]	18 (36.7)	6 (28.6)

SBP: systolic blood pressure, DBP: diastolic blood pressure.

TABLE 6. SUMMARY OF REPORTED ADVERSE EVENTS

Adverse event	*Number of events*	*Severity*
Events possibly caused by study drug		
• Angio-oedema	2	Mild/moderate
• Urinary retention	1	Moderate
• Gout	1	Severe
• Dry cough	2	Severe
• Repetitive epistaxis	1	Severe
Events unlikely to have been caused by study drug		
• Asthenia and pain	1	Severe

TABLE 4. COMPARISON OF BLOOD PRESSURES BEFORE AND AFTER COMMENCEMENT OF STUDY DRUG IN PATIENTS WHO RECEIVED MONOTHERAPY AND THOSE WHO RECEIVED DUAL OR MORE THERAPY

	Monotherapy			*Dual or more therapy*		
	*Visit 1 (*n = *267)*	*Visit 2 (*n = *247)*	*Visit 3 (*n = *238)*	*Visit 1 (*n = *142)*	*Visit 2 (*n = *131)*	*Visit 3 (*n = *132)*
SBP (mmHg)	168.1 ± 19.1	141.9 ± 19.4	134.3 ± 14.8	170.1 ± 20.0	147.1 ± 18.0	139.3 ± 15.8
Δ SBP (mmHg)	NA	–25.3*	–32.9*	NA	–23.0*	–30.4*
DBP (mmHg)	102.0 ± 11.7	88.2 ± 12.1	83.3 ± 9.6	102.4 ± 11.8	89.6 ± 10.7	86.7 ± 9.6
Δ DBP (mmHg)	NA	–14.1*	–18.8*	NA	–13.3*	–16.0*

SBP: systolic BP, DBP: diastolic BP, Δ SB: change in systolic BP from baseline, Δ DBP: change in diastolic BP from baseline, NA: not applicable *$p < 0.001$.

inhibitor ramipril in black Africans.

Although there is evidence to suggest that ACE inhibitors lower BP to a lesser extent when used as monotherapy in African-Americans,[15,16] the ASTRAL study has demonstrated that the combination of ACE inhibitor and thiazide diuretic was effective in controlling BP in black Africans. This is given that a high number of the patients reached target goals of BP control despite a substantial number of them either initially not receiving pharmacological treatment (8.9%) or being on a single agent for BP control (61.9%). The lower attainment of BP goals in the diabetic group, as was also indicated by the logistic regression analysis, may be an indication of the lower target and the degree of diabetic end-organ damage, including nephropathy.

Similar results were reported from South Africa where enalapril was ineffective as monotherapy but the addition of either a diuretic or reserpine dramatically increased BP control rates.[17] Underscoring the efficacy of fixed-dose ramipril/HCTZ in this study was the sustained and significant change in SBP and DBP from week zero to week eight and the fact that most of the patients remained on standard or half-standard dose of ramipril/HCTZ throughout the study duration.

In addition to its effects on BP, ramipril offers additional benefits on target-organ protection in patients of African descent. In the African-American Study of Kidney Disease (AASK),[18] ramipril was superior to amlodipine on renal outcomes in patients with hypertensive nephrosclerosis for comparable BP control. Other studies like HOPE[19] and AIRE[20] (although not directly linked to African patients because of small numbers of black patients enrolled), showed important benefits of ramipril in patients at high CV risk or with cardiac failure, respectively. The present study was however not designed to assess other additional benefits of ramipril.

During the ASTRAL study period, there were eight episodes of reported adverse events by six patients who were on either half-standard or standard therapy, suggesting that the adverse events may not have been dose related. It is nonetheless not surprising that facial oedema and dry cough were the two most common, given that these two, together with hyperkalaemia, hypotension and renal dysfunction, are known and commonly reported adverse effects of ACE inhibitor use.

In the HOPE study,[19] reasons for discontinuation of the study were cough (7.3%), hypotension (1.9%) and angio-oedema (0.4%). However, given the short duration of the present study, it may be difficult to conclude that the study drug is safe with a small adverse-events profile, even though there has been a relatively low frequency of reported adverse events. A particular concern for clinicians in Africa may be the increased risk of angio-oedema[21] and deaths[22] reported with enalapril in African-Americans compared to whites, suggesting that there may be racial differences in the predilection to angio-oedema with the use of ACE inhibitors. In the ASTRAL study, the incidence of ACE inhibitor-related angio-oedema was 0.45%, which closely approximates the incidence reported in the HOPE study.[19]

One limitation of the ASTRAL study has been the inability to measure or document changes in serum electrolytes and certain metabolic parameters, such as sodium, potassium, uric acid and glucose, which are known to be affected by thiazide diuretics. The modern tendency is for low-dose HCTZ (12.5 mg) to be recommended to avoid these metabolic complications and this has been incorporated into recent guidelines.[23] However HCTZ 12.5 mg as monotherapy has never been shown to improve outcomes and has a very weak anti-hypertensive activity in African patients.[16] The higher dose of HCTZ (25 mg) offers more effective antihypertensive activity, particularly in combination with inhibitors of the renin–angiotensin system.

There are also concerns, particularly regarding the increased incidence of new-onset diabetes with the higher dose. This is a controversial topic but it has never been shown in a large outcome study that new-onset diabetes worsens outcomes.[24] Although there was no measurement of blood glucose in this study there were no reported cases of new-onset diabetes.

A few patients were titrated upwards to ramipril 10 mg/HCTZ 50 mg for better BP control and although no significant adverse effects were reported, this raises some concerns about evaluating drug efficacy against its potential adverse effects, particularly electrolyte imbalances. Although this high dose of HCTZ has been used in major outcome studies, we would rather recommend the addition of alternative anti-hypertensive agents to achieve BP control until further safety information is available. In this study, the majority of patients did not require more than 25 mg HCTZ in the fixed-dose combination to achieve BP control.

Conclusion

Fixed-dose combination of ramipril/HCTZ is an effective, tolerable anti-hypertensive agent with a good safety profile, which can be used to control BP in black Africans. This combination may be more effective in non-diabetics than patients with diabetes mellitus. Extended study with this combination is still needed to assess its long-term efficacy and safety.

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Serum high-sensitivity C-reactive protein, amyloid-associated protein and N-terminal proBNP levels do not predict reversible myocardial ischaemia

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Summary

Aim: **The aim of this study was to detect any relationship between serum high-sensitivity C-reactive protein (hs-CRP), serum amyloid-associated protein (SAA) and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, and reversible myocardial ischaemia during cardiovascular exercise tests and to determine whether these biomarkers could predict transient myocardial ischaemia.**

Methods: **Ninety-six patients (36 women, 60 men, mean age 57 ± 8.5 years) were included in the study. Venous blood samples were taken from patients before and 15 minutes after exercise testing. SAA and hs-CRP were analysed using immunonephelometric assays (Dade-Behring, BN II, Marburg, Germany). NT-proBNP (pg/ml) was determined using the immulite 1 000 chemiluminescence immunoassay system (Siemens Medical Solution Diagnostics, Deerfiled, USA). Forty-eight patients (18 women, 30 men) with positive exercise tests were allocated to the exercise-positive group and 48 (18 women, 30 men) with negative exercise tests were put in the exercise-negative group. Coronary angiography was performed on all patients in the exercise-positive group.**

Results: **There was no difference between the levels of hs-CRP, SAA and NT-pro-BNP before and after exercise testing in both of the exercise groups.**

Conclusion: **Serum levels of hs-CRP, SAA and NT-proBNP could not predict the occurrence of reversible myocardial ischaemia during exercise. Large-scale clinical studies are needed to clarify the status of hs-CRP, SAA and NT-proBNP with exercise.**

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Keywords: brain natriuretic peptide, coronary artery disease, exercise, ischaemia

Submitted 15/12/09, accepted 22/4/10

Cardiovasc J Afr 2010; **21**: 85–89 www.cvja.co.za

DOI: CVJ-21.027

As a response to inflammatory cytokines, high-sensitivity C-reactive protein (hs-CRP) is synthesised mainly by the liver and to a lesser extent by macrophages and blood vessel walls. hs-CRP circulates freely in the plasma because there are no specific transporters for it.[1,2] It has been shown that hs-CRP is a powerful predictor of cardiovascular adverse events and mortality in unstable coronary heart disease.[3-5] However, its role in predicting transient myocardial ischaemia in stable coronary heart disease is not clear. While some studies found a strong relationship between serum hs-CRP levels and reversible myocardial ischaemia in exercise electrocardiographic testing,[6] others did not find such a relationship.[7,8]

Serum amyloid-associated protein (SAA) is an acute-phase reactant and its concentration can reach up to 1 000-fold of the normal plasma concentration in the presence of inflammation. SAA is mainly synthesised by the liver.[9] Serum levels of SAA rise with obesity, diabetes and the metabolic syndrome.[10,11] Some studies point to a positive correlation between SAA and angiographically proven coronary artery disease, and serum concentration of SAA is reported to be a powerful predictor of cardiovascular events.[12,13] It has been shown that patients with a high SAA concentration have more active atherosclerotic disease,[14] but the relationship between serum SAA levels and transient myocardial ischaemia during exercise is not known.

B-type natriuretic peptide (BNP) is synthesised by the ventricular myocardium as a response to wall stress and is not stored.[15] Myocardial ischaemia activates the pre-proBNP gene expression and secretion. Especially newly synthesised proBNP is secreted from the myocardium in response to ischaemia.[16] BNP is the biologically active form and N-terminal proBNP (NT-proBNP) is the inactive form of proBNP. In one study, increase in serum BNP levels during electrocardiographic exercise testing was found in patients with stable angina pectoris. Also, the rise in serum BNP levels was correlated with the size of the ischaemic myocardium, assessed with positron emission tomography.[17] In patients with angiographically proven coronary artery disease, serum NT-proBNP levels were related to the extent and severity of coronary artery disease.[18]

The purpose of this study was to detect any relationship between serum hs-CRP, SAA and NT-proBNP levels, and reversible myocardial ischaemia during cardiovascular exercise testing, and to determine whether these biomarkers could predict transient myocardial ischaemia.

Methods

Ninety-six patients (36 women, 60 men, mean age 57 ± 8.5 years) were included in the study between March and May 2009. The study group comprised patients who had visited our outpatient clinic and electrocardiographic exercise testing was planned to detect ischaemia. All patients had a history of either exercise-induced angina or atypical angina. Patients with previous myocardial infarction, previous revascularisation, chronic kidney failure, known malignancy, serious peripheral arterial disease, heart failure, valvular heart disease, previous cerebrovascular accident, known chronic inflammatory conditions and with active infectious diseases were excluded from the study. The local ethics committee approved the study and informed written consent was obtained from all patients.

Exercise testing

According to the current guidelines, patients discontinued medicines that could affect the exercise testing 48 hours before the test.[18] Patients performed the exercise test after a three-hour fast and they were not allowed to drink tea/coffee or smoke before the test. All patients underwent a standard exercise stress test using the modified Bruce protocol.

Blood pressure, heart rate and 12-lead ECGs were recorded at rest, during each stage of exercise, at peak exercise, and for at least five minutes in the recovery phase. The ECG and ST-segment depression were continuously displayed and measured automatically by a computer-assisted system (Marquette-Case treadmill system, General Electric, Milwaukee, USA) in all 12 leads.

The subjects were exercised until one of the end-points was reached: age-specific target heart rate, or the development of symptoms necessitating termination of the test. Patients were encouraged to perform to their maximum effort and symptoms that developed during the test were recorded. The development of 0.10 mV (1 mm) or more of J-point depression measured from the PQ junction, with a relatively flat ST-segment slope (e.g. less than 0.7–1 mV/sec), depressed 0.10 mV or more 80 ms after the J point (ST 80) in three consecutive beats, with a stable baseline, was considered to be an abnormal response.

Criteria for a positive exercise test were determined as an abnormal ST-segment response, or other criteria for positive exercise testing [drop in systolic blood pressure > 10 mmHg from baseline blood pressure despite an increase in workload, when accompanied by other evidence of ischaemia; moderate to severe angina; sustained ventricular tachycardia; ST elevation (≥ 1.0 mm) in leads without diagnostic Q waves (other than V1 or avR)].[18] Patients with a positive exercise test were placed in the positive exercise group. Patients who did not meet the positive criteria were not considered to have ischaemia and were put in the negative exercise group.

In order to detect the ischaemic aetiology, coronary angiography was performed on an outpatient basis on all patients in the positive exercise group on another suitable day. Stenosis that reduced the lumen diameter by 50% in a coronary artery was accepted as a haemodynamically significant lesion.

Blood sampling and biochemical analysis

Venous blood samples were taken from the antecubital veins of patients before and 15 minutes after the exercise test. Blood samples were taken in standard heparinised and non-heparinised tubes. Samples were centrifuged at 3 500 rpm for 10 minutes. Care was taken with the blood samples so as not to become lipaemic or haemolysed. Centrifuged heparinised blood samples were kept at –20°C.

SAA and hs-CRP were immediately assayed from the non-heparinised blood samples using immunonephelometric assays (Dade-Behring, BN II, Marburg, Germany). The reference concentration for SAA was < 5 mg/l and for hs-CRP it was < 3mg/l. After collecting the samples, NT-proBNP (pg/ml) was assayed using the immulite 1 000 chemiluminescence immunoassay system (Siemens Medical Solution Diagnostics, Deerfiled, USA).

Statistical analysis

SPSS for Windows version 13.0 was used for statistical analysis. Student's t-test was used for comparison of mean values; $p < 0.05$ was accepted as significant.

Results

Of the 96 patients, 48 (18 women, 30 men) with positive exercise tests were allocated to the positive exercise group and 48 (18 women, 30 men) with negative exercise tests were put into the negative exercise group. There was a statistically significant difference between the two groups for smoking, hyperlipidaemia, hypertension and family history of coronary heart disease (Table 1).

Mean exercise duration was significantly longer in the negative exercise group than in the positive exercise group (11.5 ± 1.1 vs 8.9 ± 2.6 min, $p < 0.001$). Metabolic equivalents (METs) were also higher in the negative exercise group than in the positive group (12.3 ± 1.5 vs 9.5 ± 2.6, $p < 0.001$). There was no difference between the levels of hs-CRP, SAA and NT-proBNP before and after exercise testing in both groups (Table 2).

The results of coronary angiography in the positive exercise group of patients were as follows: there was single-vessel disease in 21 patients, two-vessel disease in 11 patients, isolated side-branch disease in five patients, triple-vessel disease in four patients, left main coronary artery disease in two patients, left main plus triple-vessel disease in two patients, coronary artery ectasia in two patients, and spontaneous dissection of one coronary artery in one patient.

Medical follow up was chosen in 28 patients as the main

TABLE 1. DEMOGRAPHIC FEATURES AND RISK FACTORS OF PATIENTS

	Positive exercise testing (n = 48) (%)	*Negative exercise testing (n = 48) (%)*	p-*value*
Age (years)	57 ± 10.0	57 ± 7.0	> 0.05
Gender (female/male)	18/30	18/30	> 0.05
BMI (kg/m^2)	27.7 ± 3.7	28.9 ± 4.2	> 0.05
Diabetes mellitus	16/48 (33)	14/48 (29)	> 0.05
Current smoker	30/48 (62)	18/48 (37)	< 0.03
Hypertension	44/48 (91)	18/48 (37)	< 0.001
Hyperlipidaemia	44/48 (91)	26/48 (54)	< 0.001
Family history	41/48 (85)	16/48 (33)	< 0.001

BMI: body mass index.

TABLE 2. SERUM HS-CRP, SAA AND NT-proBNP LEVELS BEFORE AND AFTER EXERCISE TESTING

	*Positive exercise testing (*n = *48)*		*Negative exercise testing (*n = *48)*		
	Pre-test	*Post-test*	*Pre-test*	*Post-test*	p-*value*
Hs-CRP (mg/l)	4.1 ± 6.2	4.9 ± 6.5	1.9 ± 1.3	2.7 ± 1.7	> 0.05
SAA (mg/l)	8.4 ± 12.3	10.0 ± 14.0	5.8 ± 4.2	6.2 ± 4.1	> 0.05
NT-proBNP (pg/ml)	175.1 ± 392.3	201.5 ± 461.6	92.2 ± 130.5	102.5 ± 139.2	> 0.05

hs-CRP: high-sensitivity C-reactive protein, SAA: serum amyloid-associated protein, NT-proBNP: N-terminal proBNP.

therapeutic modality, whereas 14 patients underwent percutaneous coronary intervention and were discharged one day after the procedure with appropriate medication. In six patients, an aorto-coronary bypass grafting operation was successfully performed. No surgery-related complications occurred and all of the patients were discharged uneventfully.

Discussion

In this study, we observed a slight non-significant rise in the serum levels of hs-CRP, SAA and NT-proBNP with exercise. Although the increase in serum SAA, hs-CRP and NT-proBNP levels during exercise testing was slightly more in the positive exercise group, the difference was not significant. We concluded that serum levels of hs-CRP, SAA and NT-proBNP could not predict the occurrence of reversible myocardial ischaemia during exercise.

Shehadeh *et al*. reported that there was no relation between hs-CRP and transient myocardial ischaemia in patients with a history of chronic heart failure or previous myocardial infarction.[7] They also found that exercise duration was longer in patients with lower levels of hs-CRP. In our study, although basal serum hs-CRP levels were the same in the two groups, the exercise capacity of the non-ischaemic group was better than in the ischaemic group. Veleska *et al*. could not find any relationship between serum hs-CRP levels and exercise testing results in a study that included 200 patients with positive exercise tests.[8] On the other hand, Cosin-Sales *et al*. reported a correlation between serum hs-CRP levels and ST-segment depression during exercise testing with Holter monitoring, and the frequency of angina episodes in patients with typical chest pain and normal coronary angiograms.[6] Therefore, the relationship between hs-CRP and reversible myocardial ischaemia was not as clear as in unstable coronary artery disease and needs to be clarified in large-scale studies.

High-density lipoprotein (HDL) is the main carrier of SAA in plasma. In cases of low HDL status, SAA is carried by the other apolipoproteins.[19-21] SAA may comprise up to 80% of HDL during inflammation, which results in deterioration of the anti-atherogenic properties of HDL.[19-21] Ogasawara *et al*. reported that HDL molecules rich in SAA are a risk factor for cardiovascular diseases, therefore the SAA/LDL complex was found to be directly related to high cardiovascular risk.[22]

In both groups in our study, serum SAA levels increased slightly after exercise testing but there was no significant difference. The increase in SAA levels seemed not to be associated with myocardial ischaemia. We also could not find any study addressing the relationship between SAA and transient myocardial ischaemia in the literature.

Early studies reported a decrease in serum inflammatory biomarker levels in subjects who exercised regularly.[23] However, during short, sudden exercise, the immune system becomes activated and inflammatory biomarker levels elevate in the serum. This mechanism has not been clarified.[23] The possible mechanisms are: muscle damage during exercise, new developing oxidative stress as a response to the increase in oxygen demand with the forced usage of muscles, and increased interleukine-6 (IL-6) synthesis in muscles.

Firstly, the increase in serum CRP and SAA levels during exercise may be due to increased synthesis of IL-6. In addition, leucocyte counts increase during exercise.[24] As a result, these changes may trigger immune system activation and increased levels of acute-phase reactants. In our study, serum SAA levels increased, as did serum hs-CRP levels after exercise in both the ischaemic and non-ischaemic groups. But we felt these elevations were as a result of exercise-induced immune system activation and did not reflect myocardial ischaemia.

NT-proBNP is the inactive form of BNP. Like other natriuretic peptides, the serum concentration of NT-proBNP increases as a response to increased left ventricular myocardial wall stress.[25,26] NT-proBNP levels increased in patients with disorders causing left ventricular diastolic dysfunction, but this increase in NT-proBNP was not as much as that seen in left ventricular systolic dysfunction.[27]

In recent years, increased NT-proBNP synthesis has been shown as a response to myocardial ischaemia. In addition, it has also been shown that increases in NT-proBNP levels were related to the extent and severity of the coronary artery disease.[28] Serum NT-proBNP was found to be a strong predictor for future cardiovascular events in patients with stable angina pectoris.[29]

Some studies were designed for detecting the correlation between NT-proBNP and transient myocardial ischaemia. Kurz *et al*. found that baseline NT-proBNP levels were higher in patients with transient ischaemia; however there was no correlation between NT-proBNP levels and ischaemia after exercise testing.[30] In another study which was done with myocardial perfusion scintigraphy, Staub *et al*. reported that NT-proBNP levels before and after exercise were significantly higher in patients who developed transient ischaemia.[31] Sabatin *et al*. and Foote *et al*. also reported similar results.[32,33] On the other hand, other studies reported contradictory findings.[34,35] In a study, before and after exercise testing, serum NT-proBNP levels were studied hourly for six hours and NT-proBNP levels were not found to be correlated with myocardial ischaemia.[36]

In our study, we could not find any relationship between transient myocardial ischaemia and serum NT-proBNP levels before and after exercise testing. In both ischaemic and non-ischaemic patients, serum NT-proBNP levels increased slightly after exercise testing. This might have been caused by a mechanism other than ischaemia. In a study on healthy adults, an increase in serum NT-proBNP levels was shown after electrocardiographic exercise testing.[37] It was concluded that these increases after exercise test-

ing were due to elevated cardiac load and increased ventricular wall tension.[38,39]

The most important limitation of our study was the small number of patients. This was due to us excluding patients with known coronary artery disease and prior revascularisation. Another limitation was that it was a single-centred study reflecting a local area.

Conclusion

In our study we found that there was no relationship between exercise-induced transient myocardial ischaemia and serum hs-CRP and SAA levels as inflammatory biomarkers, and serum NT-proBNP levels as a non-inflammatory biomarker. All three biomarkers increased with exercise for different reasons but these elevations were not related to transient myocardial ischaemia. Large-scale clinical studies are needed to clarify the status of hs-CRP, SAA and NT-proBNP with exercise.

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Case Reports

Isolated left ventricular non-compaction with normal ejection fraction

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Summary

Isolated left ventricular non-compaction (LVNC) is a genetic disease that is being increasingly recognised in patients presenting with heart failure of unknown origin. In this case report, we describe a patient with classic LVNC without clinical heart failure and with normal left ventricular ejection fraction.

Keywords: normal systolic function, isolated left ventricular non-compaction

Submitted 18/11/09, accepted 14/3/10

Cardiovasc J Afr 2010; **21**: 90–93 www.cvja.co.za

DOI: CVJ-21.017

A 37-year-old lady presented with atypical chest pain and was referred by her primary physician for an echocardiogram to evaluate her cardiac structure and function. On direct questioning, she had no symptoms to suggest cardiac dysfunction in particular, nor did she have any symptoms suggestive of an arrhythmia. Her physical examination was unremarkable except for tenderness over her left costal cartilages, in keeping with costochondritis. The resting electrocardiogram was normal.

An echocardiogram revealed that she had normal cardiac dimensions measured at the base of the heart, with a global ejection fraction of 60%. There were no regional wall abnormalities but she had marked trabeculation involving the apex, apicolateral and apico-inferior walls (Figs 1, 2, 4). Deep intra-trabecular recesses with flow were demonstrated using colour Doppler (Figs 3, 5). On the Jenni criteria, the ratio of non-compacted to compacted myocardium was greater than 2, measured at end-systole in the parasternal short-axis view. Mitral inflow Doppler revealed a pseudo-normalisation pattern with a diminished E′ on tissue Doppler, suggesting grade 2 diastolic dysfunction (Fig. 6). The right ventricle was normal. The rest of the heart was normal structurally and functionally.

Coronary angiography revealed no anomalies, with normal epicardial coronary anatomy and flow. The left ventricular angiogram revealed marked trabeculation with dye staining in the same areas noted on the echocardiogram (Fig. 7). The ejection fraction was 65%. A Holter electrocardiogram was normal.

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A final diagnosis of isolated left ventricular non-compaction with preserved left ventricular systolic function and moderate diastolic dysfunction was made. The patient was placed on warfarin.

Discussion

Isolated LV non-compaction of the myocardium

Isolated LV non-compaction was classified as a genetic cardiomyopathy in the 2006 classification of cardiomyopathy, and

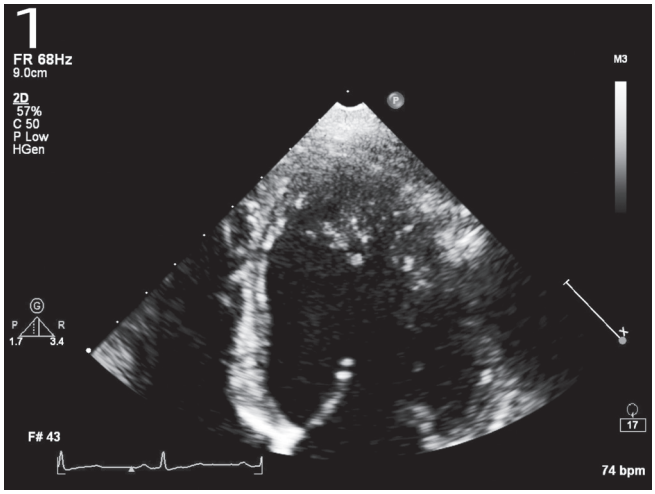

Fig. 1. Apical four-chamber view in diastole demonstrating trabeculation of the apex and apicolateral wall.

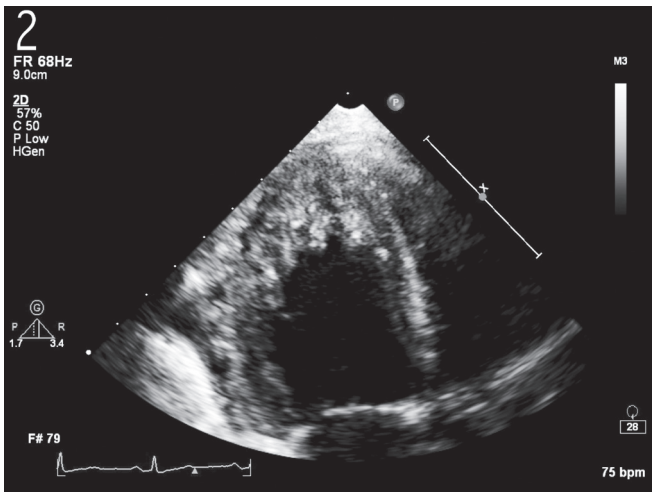

Fig. 2. Apical two-chamber view in end-systole demonstrating the marked trabeculation of the apex and apico-inferior wall with the underlying thin epicardial compacted area.

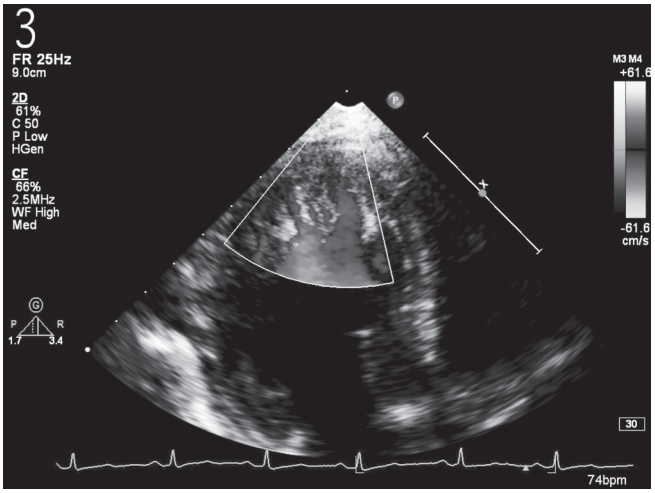

Fig. 3. Apical two-chamber in diastole demonstrating flow within the trabeculae.

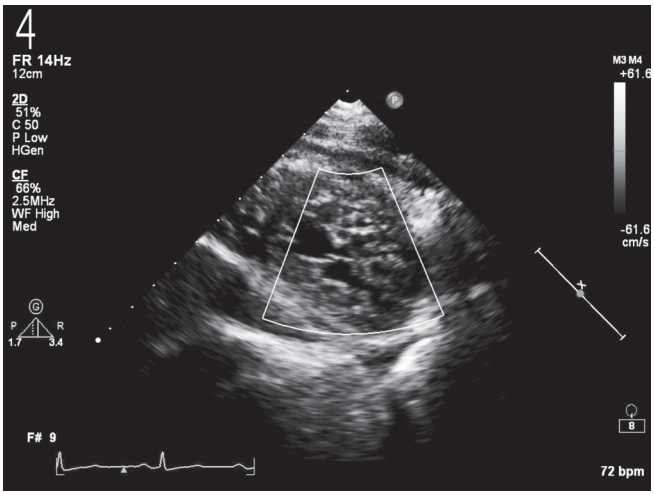

Fig. 4. Short-axis view at the apex demonstrating marked trabeculation.

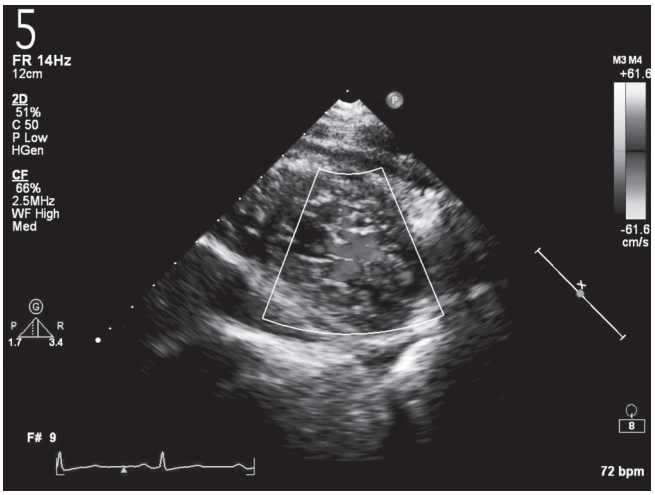

Fig. 5. Short-axis view at the level of the apex demonstrating flow within the trabeculae.

was first described as an entity in 1990 by Chin *et al*.[1,2] It occurs because of an arrest in the normal embryonic process of myocardial compaction, which occurs after the fourth week of life. This results in the persistence of trabeculae together with

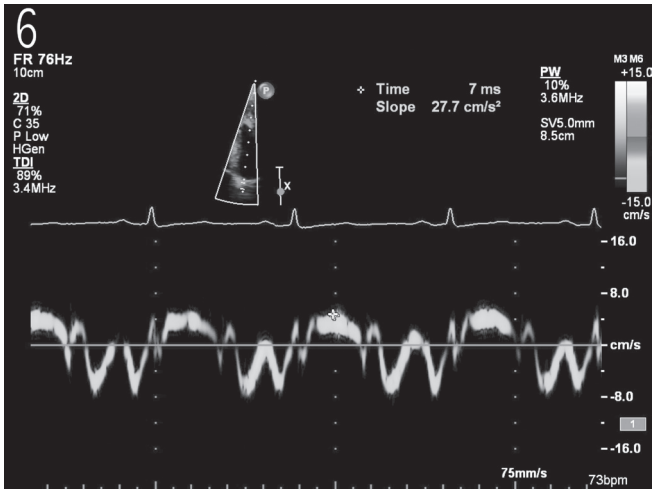

Fig. 6. Tissue Doppler demonstrating a reduced E′ in keeping with diastolic dysfunction.

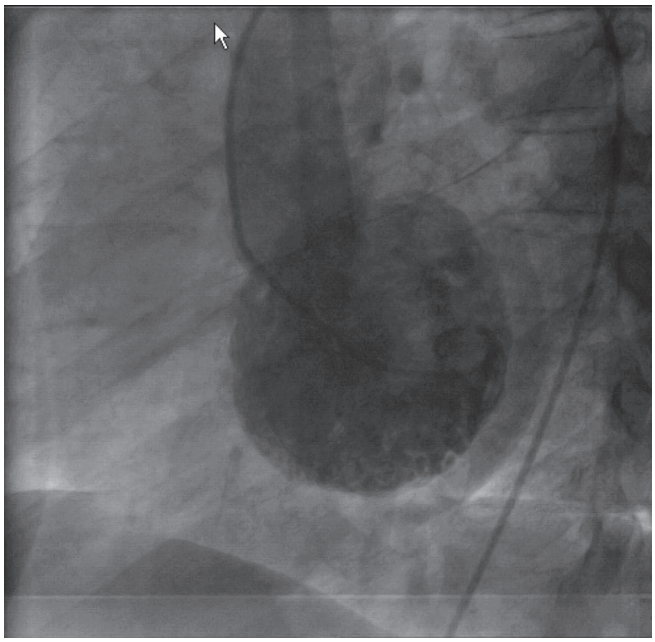

Fig. 7. Left ventriculargram demonstrating marked trabeculation with dye staining in apex and lateral wall.

adjacent deep intra-trabecular recesses filled with blood. The term 'isolated' is reserved for situations in which there are no associated cyanotic congenital heart disease, obstructive intracardiac lesions, anatomical valvular abnormalities or associated coronary anomalies. This process may involve the right ventricle in less than 50% of cases.[3]

The diagnosis on echocardiography is suspected by the presence of more than three trabeculations, usually in the apex, apicolateral and apico-inferior walls. The apical and mid-ventricular walls of the inferior and lateral walls can be involved in up to 80% of cases. Deep intra-trabecular recesses accompany this, and the presence of blood flow within these recesses on colour Doppler is essential. The Jenni criteria utilise these features as the basis for diagnosis on two-dimensional echo, emphasising that on parasternal short axis, the ratio of the non-compacted to compacted layer should be greater than 2 at end-systole.[4,5]

Recently, a few case reports suggested that three-dimensional echo may improve diagnosis in subtle cases.[6] Contrast echo is

useful to demarcate endocardial borders and visualise intra-trabecular recesses. Other diagnostic modalities that may aid diagnosis are MRI and invasive left ventricular angiography.

The clinical presentation revolves around three key features, namely heart failure, arrhythmias and left ventricular thrombus formation. It is important to note that the clinical manifestation and age of presentation are variable.[1,2] Heart failure is commonly the basis of systolic dysfunction, which may be related to micro-vascular ischaemia and very uncommonly patients may have only diastolic dysfunction.[7]

Arrhythmias, particularly ventricular tachyarrhythmias are a cause of sudden death and may mandate the implantation of an ICD as primary prevention in patients with severe systolic dysfunction. Thrombus formation occurs because of stasis within the trabeculae and cardio-embolism can occur in particular in the cerebral, coronary and mesenteric circulation. Hence oral anticoagulation with adequate INR monitoring is essential and is suggested even in the absence of documented thrombus formation.

Other clinical associations include facial dysmorphisms and neuromuscular abnormalities. In one series, familial disease was found in up to 44% of cases. Klaasen *et al*. have subsequently described various sarcomeric mutations that may be found in isolated left ventricular non-compaction.[8]

This particular clinical case highlights the importance of paying attention to the heart apex on echocardiography, since under normal circumstances this is the thinnest portion of the ventricle. The presence of blood flow within the trabecular recesses differentiates the findings of non-compaction from apical hypertrophic cardiomyopathy, cardiac tumours and thrombus formation. Furthermore, it is very uncommon to find more than four trabeculae in a normal left ventricle.[9] The spectrum of non-compaction with normal ejection fraction by conventional echo indices is uncommon and was the first case noted in our clinic.

Isolated LV non-compaction with normal ejection fraction

A review of the literature reveals that in the first case series described by Chin *et al*. in 1990, 63% of patients had depressed LV systolic function.[2] A recent analysis of the Mayo Clinic echo database 2001–2006 revealed that 77% of the 30 patients who fulfilled the criteria for isolated left ventricular non-compaction had a low ejection fraction.[10]

In one of the largest series that included 78 patients with isolated LV non-compaction diagnosed by the Jenni criteria, Steffel *et al*. identified an ejection fraction greater than 50% on left ventricular cine angiography in 32% of their patients.[11] Furthermore, in children, isolated LV non-compaction may present initially as a restrictive cardiomyopathy.[12]

Therefore it is clear that isolated LV non-compaction can be found in patients with normal ejection fraction. Whether these patients progress to overt systolic dysfunction is not well described in the current literature but this may be possible as part of a spectrum related to chronic microvascular ischaemia with secondary fibrosis and remodelling.

The prognosis of patients with non-compaction is variable, although the literature suggests a poor survival, with one large series having only 60% of patients at six years who had not died or undergone cardiac transplantation.[3,13,14] The Mayo group have suggested from an analysis of their database that the morbidity and mortality of patients with isolated LV non-compaction may be related to the presence of left ventricular dysfunction and not the non-compacted myocardium.[10] Furthermore, although their follow up was only 2.5 years, no deaths were observed in the subgroup with normal ejection fraction, suggesting that ICD therapy may be reserved for patients who have left ventricular dysfunction.

Therefore it seems that the measurement of ejection fraction is a powerful marker of overt systolic dysfunction and is associated with a poorer prognosis in these patients. It is clear that a normal ejection fraction does not imply normal systolic function and techniques such as tissue Doppler imaging or speckle tracking may be able to detect abnormal systolic myocardial mechanics when the ejection fraction is normal. These abnormalities can be demonstrated in conditions such as amyloid and hypertrophic cardiomyopathy where ejection fraction can be normal despite overt regional systolic dysfunction.

In amyloid cardiomyopathy there is profound depression of longitudinal systolic strain despite a normal ejection fraction. However, regional analysis of myocardial mechanics or sub-analysis of systolic myocardial mechanics such as longitudinal strain or torsion has not been well documented in this condition. A recent report by Punn *et al*. in children utilised speckle tracking to demonstrate that that differences in contractility existed between areas that were normal compared to areas that displayed features of non-compaction.[15] They also found that greater numbers of affected segments correlated linearly and inversely with ejection fraction.

Conclusion

The optimal management of our patient besides the use of warfarin is unclear and the arrhythmic risk in this subgroup that has normal ejection fraction is probably not as sinister as it is for patients with left ventricular dysfunction. However, patients who have diastolic dysfunction are at increased risk for atrial fibrillation, which, according to a recent report, seems to alter survival.[16]

This case report highlights the entity of isolated LV non-compaction with normal ejection fraction and emphasises some important issues that need to be explored in a more scientific manner so that the practicing clinician can better manage patients diagnosed with this condition.

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Reversible myocardial stunning due to carbon monoxide exposure

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Abstract

We report on a 37-year-old patient who suffered from myocardial stunning after exposure to carbon monoxide, despite having normal coronary arteries. As myocardial ischaemia may be asymptomatic in these patients, close monitoring with serial electrocardiography and of serum cardiac enzymes and troponins is recommended.

Keywords: carbon monoxide poisoning, reversible myocardial stunning, electrocardiogram

Submitted 30/12/09, accepted 29/3/10

Cardiovasc J Afr 2011; **22**: 93–95 www.cvja.co.za

DOI: CVJ-21.021

Carbon monoxide (CO) poisoning may disturb the normal human biochemical respiratory cascade, causing ischaemic injury to tissues and cells. Such injuries to human cells have been ubiquitously documented. Carbon monoxide poisoning is rarely a cause of myocardial infarction.

CO has a higher affinity to haemoglobin than oxygen. It attaches to haemoglobin (Hb) and blocks its capacity to carry oxygen. It has been suggested that carboxyhaemoglobin causes myocardial infarction by severe generalised tissue hypoxia and a direct toxic effect on the myocardial mitochondria in patients with or without pre-existing coronary artery disease (CAD). We report on a 37-year-old woman who had reversible myocardial stunning without CAD, after exposure to CO.

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Case report

A 37-year-old woman was admitted to our emergency department with altered consciousness as a consequence of acute domestic CO poisoning from a malfunctioning stove. She had no history of tobacco use, hypertension or CAD. The rescue squad initiated artificial respiration before arrival at the emergency room. On admission, her body temperature was 37.5ºC, pulse rate was 146 beats per minute (bpm), respiratory rate was 24 breaths per min, and blood pressure was 169/72 mmHg.

The patient was semi-comatose but the remainder of the physical examination was normal. The electrocardiogram (ECG) done on admission showed sinus tachycardia with a rate of 125 bpm. The initial blood tests, including serum cardiac markers and liver-function tests were within normal limits, except for a mildly elevated white blood cell count (14 500 cells/µl). The arterial blood gas analysis showed normal values and the serum

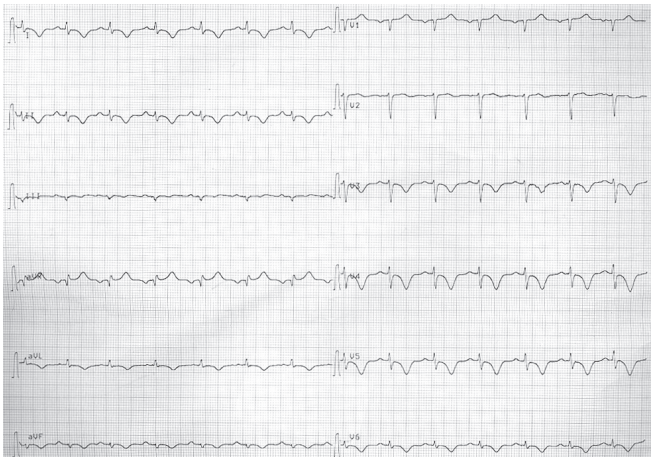

Fig. 1. Ischaemic aberrations in several leads on the ECG.

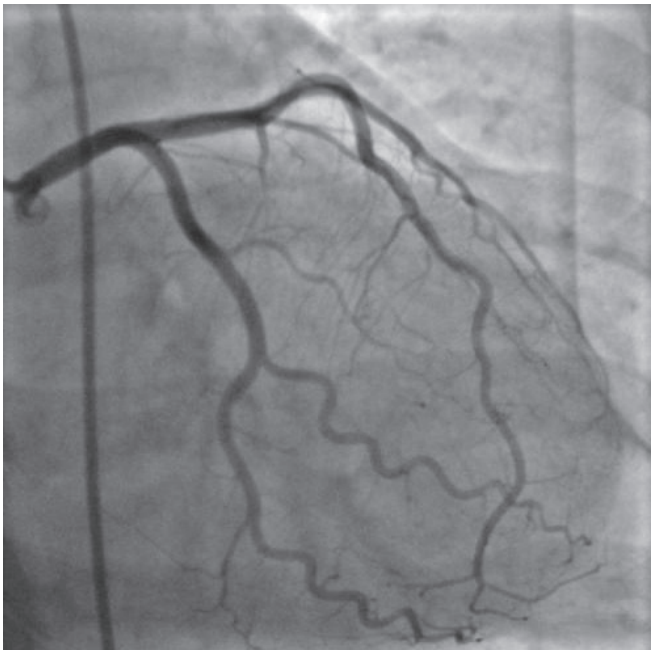

Fig. 2. Right anterior oblique coronary angiographic view with caudal angulation demonstrating normal left anterior descending and circumflex coronary arteries.

carboxyhaemoglobin level was 22%.

The patient was intubated and placed on 100% oxygen. Five hours after intubation, she was stabilised and extubated. On extubation, the patient had no angina pectoris or dyspnoea. Hyperbaric oxygen treatment was applied at 2.5 atm pressure for 150 minutes. The carboxyhaemoglobin level reduced to 2.5% by the twelfth hour post admission.

Although the patient did not have any symptoms, an ECG was done and it revealed negative T waves in leads D2, D3 and avF, ST-segment elevation on avR, 1 mm ST-segment depression and symmetric T wave negativity in leads V3–6, D1 and avL (Fig. 1). Serum cardiac markers were re-evaluated, and creatine kinase (CK) was 220 U/l, CK-MB 32 U/l and troponin I 2.6 ng/ml. The infero-apical segment was hypokinetic on echocardiography.

Coronary angiography was performed on the same day and revealed normal coronary arteries (Figs 2, 3), however the infero-apical region was also hypokinetic on left ventriculography (Fig. 4). The patient remained asymptomatic on anti-thrombotic and

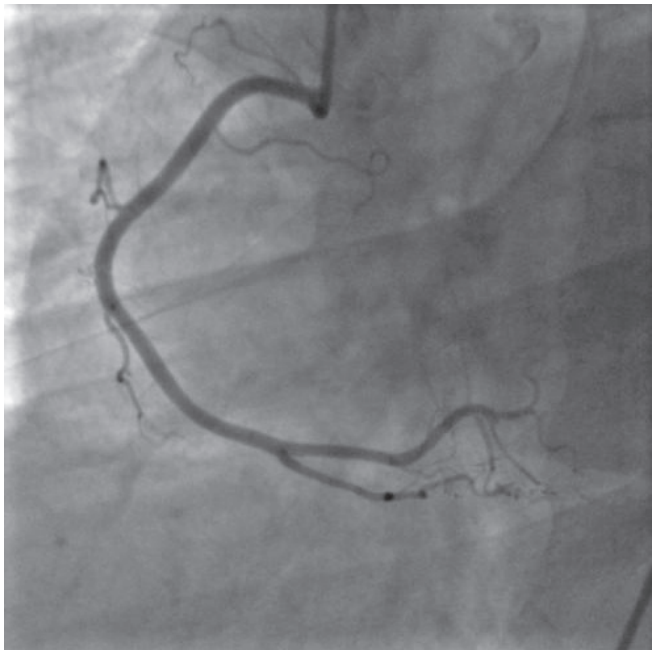

Fig. 3. Left anterior oblique coronary angiographic view showing normal right coronary artery.

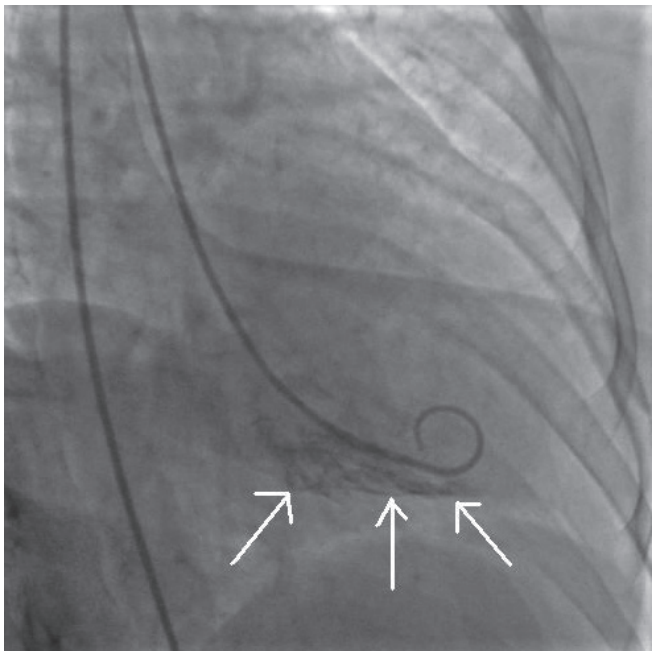

Fig. 4. Right oblique projection of left ventriculogram revealing infero-apical hypokinesia.

vasodilatator treatment. The ischaemic aberrations on the ECG normalised on the sixth day, without pathological Q waves in the inferior derivations (Fig. 5).

The patient was discharged on the sixth day without complications and a Tc-99m SPECT performed one month later did not reveal myocardial necrosis or ischaemia. A control echocardiography revealed normalisation of the abnormality in the myocardial segmentary wall motion.

Discussion

When the relationship between myocardial oxygen supply and demand is disturbed, cardiac ischaemia occurs. Although

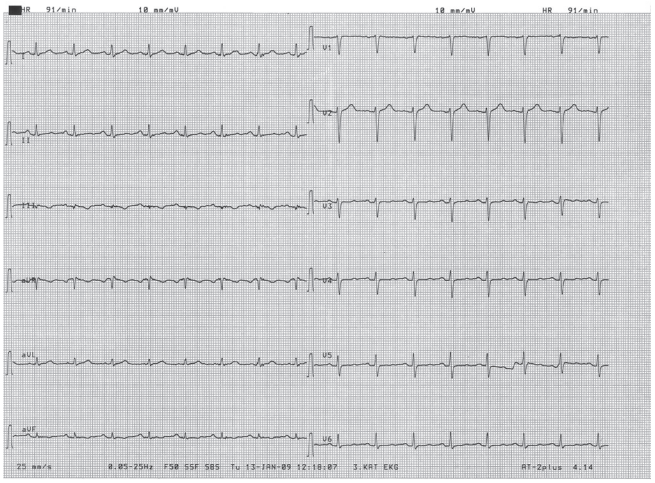

Fig. 5. Normalised ECG findings.

coronary artery disease is the most common reason for cardiac ischaemia, this does not explain the nature of the ischaemic event in many clinical situations.[1] Increased viscosity and altered platelet function have been proposed as the pathophysiological mechanisms in patients with acute myocardial infarction with normal coronary arteries.

The affinity of CO to haemoglobin is 200 to 270 times greater than that of oxygen; therefore, the formation of carboxyhaemoglobin not only decreases the amount of oxygen delivered to the tissues but also displaces the oxygen–haemoglobin dissociation curve to the left. Cardiac toxicity may result from myocardial hypoxia or from the direct toxic effect of CO on the myocardial mitochondria. An increased tendency for thrombosis and coronary vasospasm are also responsible for myocardial damage in patients with CO poisoning.[2] Myocardial infarction has been reported in patients with underlying CAD.[3] Cardiac involvement may occur promptly after exposure, or may be delayed for several days, such as in our presented case.

Electrocardiographic abnormalities have been described with acute carbon monoxide poisoning in human and animal models. These include premature atrial and ventricular contractions,[4-6] infranodal[7] and intraventricular blocks[8] and anoxic disorders in the ST segment and T wave.[9] Although in our patient, angiographically normal coronary arteries, infero-apical hypokinesia and troponin I levels suggested prolonged vasospasm or spontaneous lysis of an intracoronary thrombus as the responsible mechanism of the reversible myocardial stunning, diffuse precordial T wave negativity and ST segment elevation of avR denoted diffuse myocardial ischaemia as a concomitant mechanism.

Conclusion

Frequent ECG and cardiac enzyme monitoring is important in the management of patients with CO poisoning, as asymptomatic myocardial ischaemia and reversible myocardial stunning may be observed in the acute phase or several days later.

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Secondary intracardiac Burkitt-like lymphoma in the absence of HIV infection

AO MOCUMBI, L PAUL, L MACIEL, P SILVA, MB FERREIRA

Summary

Malignant lymphoma can involve the cardiac cavity or myocardium as a mass. Since clinical symptoms of its cardiac involvement are usually absent or non-specific, they may be undetected during life. Burkitt-like lymphoma (BLL) is a highly aggressive B-cell lymphoma with a high proliferative rate. Histopathological characteristics are considered borderline between those of classic Burkitt lymphoma and diffuse large B-cell lymphoma. Extensive cardiac involvement of BLL is rare and poorly documented in the literature.

We report the case of a child with BLL, presenting with extensive infiltration of the heart in the absence of HIV infection, and with right-sided heart failure and positional dyspnoea as the major clinical problems. We highlight the challenges for diagnosis and adequate treatment in poor settings like ours.

Submitted 13/8/09, accepted 10/3/10

Cardiovasc J Afr 2010; **21**: 96–97 www.cvja.co.za

Secondary cardiac involvement of malignant lymphoma is not uncommon, being observed in up to 25% of autopsy cases.[1] However, since clinical symptoms of this cardiac involvement are usually absent or non-specific, these tumours frequently remain undetected before death.

We report on a child who had Burkitt-like lymphoma (BLL), presenting with right-sided heart failure and positional dyspnoea as the major clinical problems.

Case report

A nine-year-old boy from a poor, remote, rural area of Mozambique was referred to our hospital with a 12-month history of thoracic pain, palpitations, shortness of breath, cough and progressive postural dyspnoea. Dyspnoea was increased in dorsal and lateral decubitus. The patient had been unsuccessfully treated with diuretics in a community health centre for nine weeks. Due to progressive deterioration of his general and nutritional status, and to the development of progressive upper thorax, neck and facial oedema, he had been admitted to a peripheral hospital for another three weeks before being transferred to our unit.

On arrival, the patient was in NYHA class IV. On physical examination he was fully conscious with dyspnoea that was aggravated in certain positions, asymmetrical facial and neck oedema, increased jugular venous pressure and cervical lymphadenopathy. The vital signs were: pulse rate 116 beats/min, temperature 38.5ºC, respiratory rate 24/min and blood pressure 100/70 mmHg. On cardiac auscultation a diastolic rumbling murmur could be heard in the tricuspid area, and the auscultation of the lungs revealed scarce rales. The abdomen was distended with considerable hepatomegaly, splenomegaly and ascites, and there was incipient oedema of the lower limbs.

The electrocardiogram showed normal sinus rhythm with no conduction anomalies or repolarisation changes. The postero–anterior chest X-ray showed marked enlargement of the superior mediastin and cardiomegaly (Fig. 1). Laboratory work up revealed a white blood cell count of 14 600 cells/µl, haemoglobin 10.3 g/dl with mean corpuscular volume 60 fl and mean concentration of haemoglobin 20.7 g/dl, platelet count 491 000 /µl, erythrocyte sedimentation rate (ESR) 16 mm, C-reactive protein (CRP) 97.4 mg/l, normal renal and liver function, spontaneous INR of 1.5 and mild hypoalbuminaemia. The HIV serology and tuberculin reaction were negative.

Transthoracic echocardiographic examination revealed a 40-mm diameter mobile homogeneous mass in the right atrium attached to the interatrial septum, partially obstructing the tricuspid valve, and hindering the filling of the right ventricle (Fig. 2a). There was infiltration of the ventricular myocardium in the interventricular septum, the interatrial septum, the area surrounding the aortic valve and the right ventricular outflow tract, without any significant obstruction (Fig. 2b). There was also a moderate fibrinous pericardial effusion. Additionally, several masses were visible in the mediastin, causing distortion of the contour of the great vessels.

An abdominal echocardiography confirmed the presence of congestive hepatomegaly, slightly enlarged spleen with numerous micronodules measuring less than a centimetre, and mild

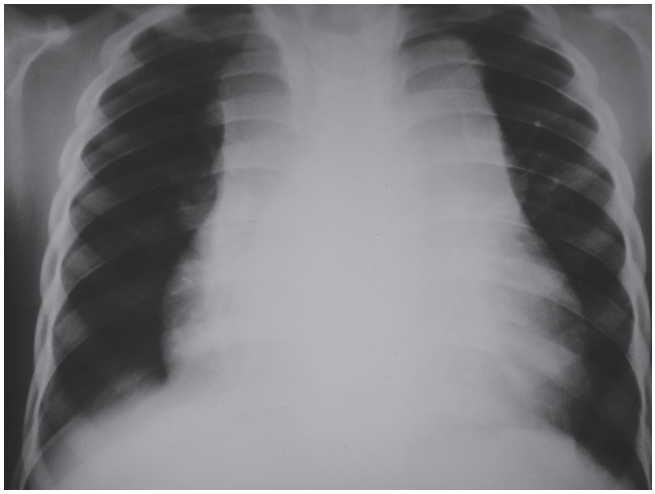

Fig. 1. Chest X-ray showing mediastinal enlargement and cardiomegaly.

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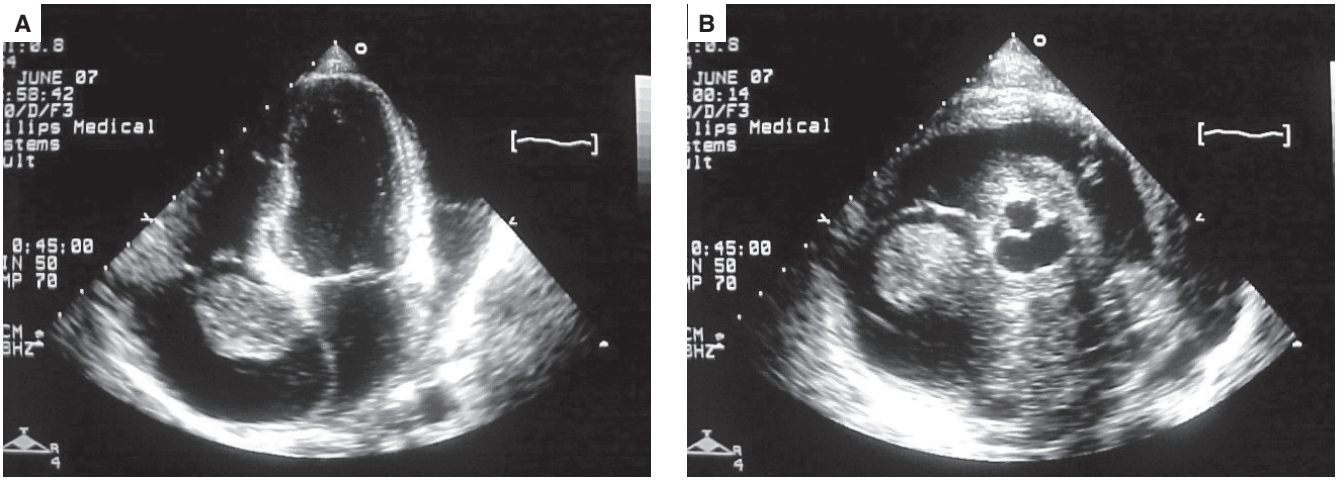

Fig. 2. Echocardiography. A. Four-chamber view showing dilatation of the right atrium, which contains a large mass attached to the interatrial septum, partially occluding the flow through the tricuspid valve. Notice the presence of moderate pericardial effusion. B. The short-axis view, at the level of the aortic valve, shows thickening of the aortic cusps and the tissue surrounding the valve. The right atrial mass is also seen attached to a thickened interatrial septum.

ascites. Computed axial tomography confirmed the presence of cervical and mediastinal lymphadenopathy which was most prominent on the right side, but there was no increase in size of the lymph nodes below the diaphragm.

The histological examination of material obtained by fine-needle aspiration biopsy over the cervical nodes revealed signs of Burkitt-like lymphoma, namely greater nuclear pleomorphism and smaller numbers of prominent nucleoli than would be expected in a classic Burkitt's lymphoma.

The child was considered to have Burkitt-like lymphoma in stage II-B. Diuretic therapy was stopped, and the patient underwent chemotherapy with the CHOP regimen using ciclophosfamide (600 mg/m^2), vincristine (1.4 mg/m^2) and doxorubicin (50 mg/m^2) IV on the first day, and prednisone (60 mg/m^2) orally for five days. His clinical condition dramatically improved, with remission of the signs of superior vena cava syndrome, reduction of the size of the intracardiac masses and remission of the biological abnormalities. The patient was discharged after three weeks but, unfortunately, was lost for follow up.

Discussion

Secondary cardiac tumours are mostly epicardial and asymptomatic,[1,2] usually being seen in the setting of widely disseminated malignancy. Less than 5% correspond to lymphomas, which may be particularly difficult to diagnose as the cause of refractory heart failure. Although recent developments in imaging techniques have contributed to progress in *in vivo* diagnosis of cardiac tumours, a high index of suspicion is usually needed.

Endemic Burkitt's lymphoma occurs in African children, usually four to seven years old, involving the bones of the jaw (and other facial bones), kidneys, gastrointestinal tract, ovaries, breast, and other extra-nodal sites; lymph node involvement is less common in this age group.[3] The differential diagnosis of Burkitt's lymphoma is broad, and precise diagnosis based on histological, immunophenotypic and genetic features remains the critical first step in planning appropriate therapy.[4] Although excision biopsy remains the preferred method for histological diagnosis of lymphoma, diagnosis and typing of lymphomas can be achieved by fine-needle aspiration cytology of subcutaneous lymph nodes,[5] a method frequently used in African settings.

Burkitt-like lymphoma is a highly aggressive B-cell lymphoma with a high proliferative rate, and histopathological characteristics considered borderline between those of classic Burkitt lymphoma and diffuse large B-cell lymphoma.[4,6] Extensive cardiac involvement of Burkitt-like lymphoma in the absence of HIV infection is rare and poorly documented in the literature.[7] Its outcome in childhood has improved with the use of short and intensive B-cell non-Hodgkin's lymphoma-directed therapy.[4,8]

Conclusion

The case we report on highlights the need to consider the diagnosis of Burkitt's lymphoma in sub-Saharan African children presenting with heart failure and intracardiac masses, even in the absence of HIV infection. It also shows that an improvement in the education of both health personal and the parents is needed to allow early diagnosis and adequate management of this condition, in order to improve its prognosis.

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Opinions in Hypertension Management

Affordable hypertension therapy for diabetic patients

Type 2 diabetes is one of the most expensive chronic diseases to treat, and in South Africa, with prescribed minimum benefits (PMB) applying to this disease, both private and public-sector funders are on the alert for cost-benefit issues. Perhaps one of the cost-benefit issues funders have missed is the current and future savings that can be made with effective anti-hypertension therapy from the outset at diabetes diagnosis.

Initial choice of anti-hypertensive defines preventative strategies

Achievement of blood pressure goals early in a patient's blood pressure-control strategy influences compliance. In a study of blood pressure treatment in a health maintenance organisation (HMO) in the United States, changes in anti-hypertensive therapy were investigated in patients whose initial therapy was angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) or calcium channel blockers (CCBs).[1]

Achievement of blood pressure goals was highest for initiators with ARBs as the therapeutic regimen (81.4%), compared with ACEIs (75.5%) and CCBs (68.9%). Adherence to therapy and need for therapeutic change was significantly least likely among ARB recipients (60%) compared with ACEI (72%) and CCB recipients (75%).

Although patients do require modification of hypertensive therapy over time, it is clear that the initial choice of anti-hypertensive therapy should be carefully considered, particularly for diabetic patients who need to reach lower blood pressure targets than non-diabetic patients.

ARBs in diabetic patient care: cost trends

There are compelling indications for the use of ARBs as the anti-hypertensive agent of choice for patients with the metabolic syndrome, in type 2 diabetes patients with microalbuminuria or albuminuria (or even before these conditions develop), and in patients who have experienced a myocardial infarction or those with left ventricular hypertrophy.[2]

Probably the largest factor affecting the appropriate use of ARBs is cost. However, experience with the generification of ACE inhibitors shows that prescribing an ARB now will be deflationary in the future.

A study in the USA of Medicaid costs[3] has shown that on generification, expenditure per ACE inhibitor claim dropped by 59% from 1991 to 2008, after adjusting for inflation for the period. This scenario of deflation in ACE inhibitor costs is likely to be repeated in the ARB environment.

Avoiding new-onset diabetes

Atrial hypertension presents a risk factor for the development of type 2 diabetes, while some anti-hypertensive therapies can promote the development of type 2 diabetes. It is well known for example that β-blockers and diuretics impair glucose metabolism, while studies indicate that the use of ACE inhibitors and ARBs lead to fewer cases of new-onset diabetes.[4]

In ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), the incidence of diabetes was diagnosed in 366 (6.7%) of the patients in the ramipril group and 399 (7.5%) patients treated with telmisartan, showing no significant differences among the groups, and demonstrating that telmisartan is effective in preventing new-onset diabetes.

In the TRANSCEND trial where telmisartan was compared with placebo, telmisartan treatment resulted in a further 15% relative risk reduction in new-onset diabetes despite high statin usage.

Preventing renal disease in diabetic patients

ACE inhibitors and ARBs that inhibit the renin–angiotensin system are recognised as first-line therapy in the prevention of diabetic kidney disease.[5]

Telmisartan provides renal benefit at all stages of the renal disease continuum in patients with type 2 diabetes. It improves endothelial function in patients with normoalbuminuria, delays the progression to overt nephropathy in patients with microalbuminuria, and reduces proteinuria in patients with macroalbuminuria.

Effectiveness of telmisartan is comparable to that of ACE inhibitors, but with greater tolerability. The effect of telmisartan on protein excretion in diabetic nephropathy appears to be better than that of losartan and equivalent to that of valsartan.

In conclusion, telmisartan offers effective hypertension therapy for diabetic patients and costs are likely to be deflationary as generification extends in the ARB market.[6]

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Simultaneous treatment of blood pressure and cholesterol beats the 'SILO' approach in lowering cardiovascular risk: results of the CRUCIAL study

The so-called 'SILO' treatment approach based on the visualisation of individual cardiovascular risk factors and resulting in one-at-a-time risk-factor treatment is less effective than the simultaneous targeting of the two major risk factors, blood pressure and cholesterol.

This has been shown in the CRUCIAL (Cluster Randomised Usual Care versus Caduet Investigation Assessing Long-term risk) study of moderately at-risk patients with no prior history of coronary heart disease (CHD) in which proactive, simultaneous treatment of blood pressure and cholesterol using a single pill (amlodipine/atorvastatin) was compared to usual care.[1]

This carefully designed, prospective, multinational, open-label trial with patients randomly designated to either proactive or usual care showed a greater relative reduction in calculated Framingham 10-year risk after 52 weeks of follow up. The mean CHD risk, which was similar at the outset of the study (actually higher in the proactive arm) dropped to 12.5% in the proactive intervention and 16.3% in the usual-care arm. The difference was also observed by week 16 and maintained through to week 52.

The subjects recruited in the study, which was conducted in Asia, Europe, the United States and South America, included typical at-risk patients. The mean age was 60 years, 42% of the 1 461 patients were diabetic with blood pressures of 150/90 mmHg and raised total cholesterol levels ≤ 6.5 mmol/l. They included equal numbers of men and women.

Patients in the usual-care group could be treated according to local protocols, which may have included atorvastatin and amlodipine. Patients in the proactive group were treated with a single-pill amlodipine/atorvastatin of 5/10-mg to 10/10-mg ratio. Subsequently, this could be raised to 5/20 mg and 10/20 mg if this dosage format was available in the country.

Therapeutic lifestyle change was given to all study participants and the clinicians were instructed to target cholesterol and blood pressure levels as recommended by either the European guidelines or the US NCEP guidelines. At the end of the study, the mean final dose of study-provided single-pill amlodipine/atorvastatin was 6.5/11 mg, respectively.

It is important to note that 58% of the patients in the proactive-intervention arm reached their JNC-7-based blood pressure goal (140/90 mmHg, or 130/80 mmHg for those with diabetes) compared to 47.5% in the usual-care arm. A greater reduction in total cholesterol and LDL cholesterol was seen at week 16 in the proactive group, which was maintained through to week 52.

The importance of this study is also reflected in the fact that the patients recruited were intentionally defined to be similar to those who participated in the ASCOT-LLA trial. This obviated the need to provide clinical outcome data in the CRUCIAL study as the long-term benefit was well defined in ASCOT using atorvastatin added to an amlodipine-based antihypertensive regimen.[2] Also, the Framingham 10-year CHD model was chosen as it included diabetes as a risk factor rather than a coronary heart disease risk equivalent. This was also consistent with the ASCOT-LLA approach.

It is important, finally, to note that the adverse event profile in the proactive-intervention arm was consistent with previous safety experience using the single-pill amlodipine/atorvastatin.

J Aalbers, Special Assignments Editor

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Drug Trends in Cardiology

Primary prevention with statins is more cost-effective

Atherosclerosis is asymptomatic and both patients and clinicians would prefer to identify the condition early in order to prevent cardiovascular events later.

Reflecting on the Canadian experience, Dr Peter Lin of the Toronto Heart Centre noted that the Canadian health authorities have supported the concept of primary prevention using powerful statins such as atorvastatin and rosuvastatin. 'Their philosophy has been to provide benefit with statins as quickly as possible so as to avoid the first cardiovascular event', he noted.

High-risk patients, according the Canadian guidelines for the diagnosis and treatment of dyslipidaemias, are defined arbitrarily as a Framingham risk score (FRS) of 20% or greater at 10 years. The Reynolds risk score is being offered as an alterative risk engine for women.[1]

'However, the guidelines point out that these risk scores are short term and if one looks at the life-time risk of men in the lowest FRS at 50 years of age, they are exposed to a lifetime risk of a major cardiovascular event of one in two. For women in this same lowest-risk category, their lifetime risk is one in four', Dr Lin pointed out.

In the Canadian system, evidence of asymptomatic atherosclerosis gained from invasive or non-invasive testing using coronary angiography, nuclear imaging, stress echocardiography or ankle-brachial index determination also puts patients into the high-risk category for cholesterol-lowering treatment prior to any actual cardiovascular events.

With regard to the role of inflammation and its biomarkers, C-reactive protein (CRP) and hs-CRP, in assessing risk for cardiovascular events, Dr Lin pointed out that for the majority of at-risk patients, hs-CRP is not needed. 'For example, patients with cardiovascular disease, raised LDL levels, prior myocardial infarction, and with diabetes already have a high-risk score on the FRS of more than 20%, and a determination of hs-CRP would not affect the clinical decision to initiate statin therapy. Hs-CRP should only be used to help define patients who clinicians do not normally treat, but who are in fact exposed to higher risk due to their inflammatory environment adversely affecting the vasculature', he stressed.

'The contribution of the JUPITER trial[2] has been to show that patients who clinicians do not normally treat gain benefit from rosuvastatin treatment, and this benefit occurs very early, in the first six months of treatment. There is clearly cost saving in this early-treatment benefit with rosuvastatin, which contrasts starkly with the experience in the 4S study with simvastatin, where benefit was only derived after a much longer period of five years', Dr Lin pointed out.

These differences in the speed and depth of protection with newer agents such as rosuvastatin argue against the approach of using simvastatin widely. 'In Canada there is hardly any simvastatin usage, despite a very cost-conscious environment. In fact, our regulatory environment encourages an early primary-prevention approach with the simple statement: 'If you are older than 50 years with two risk factors, you should be treated with an effective statin'.

J Aalbers, Special Assignments Editor

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New Dean at Stellenbosch University

Prof Jimmy Volmink has taken office as the seventh dean of the Faculty of Health Sciences. He has studied widely at overseas universities, and has an outstanding record and experience in teaching and research. We wish him great success and the courage and energy to undertake his vision of seeing the Faculty of Health Sciences advance and have a greater impact in this country and internationally.

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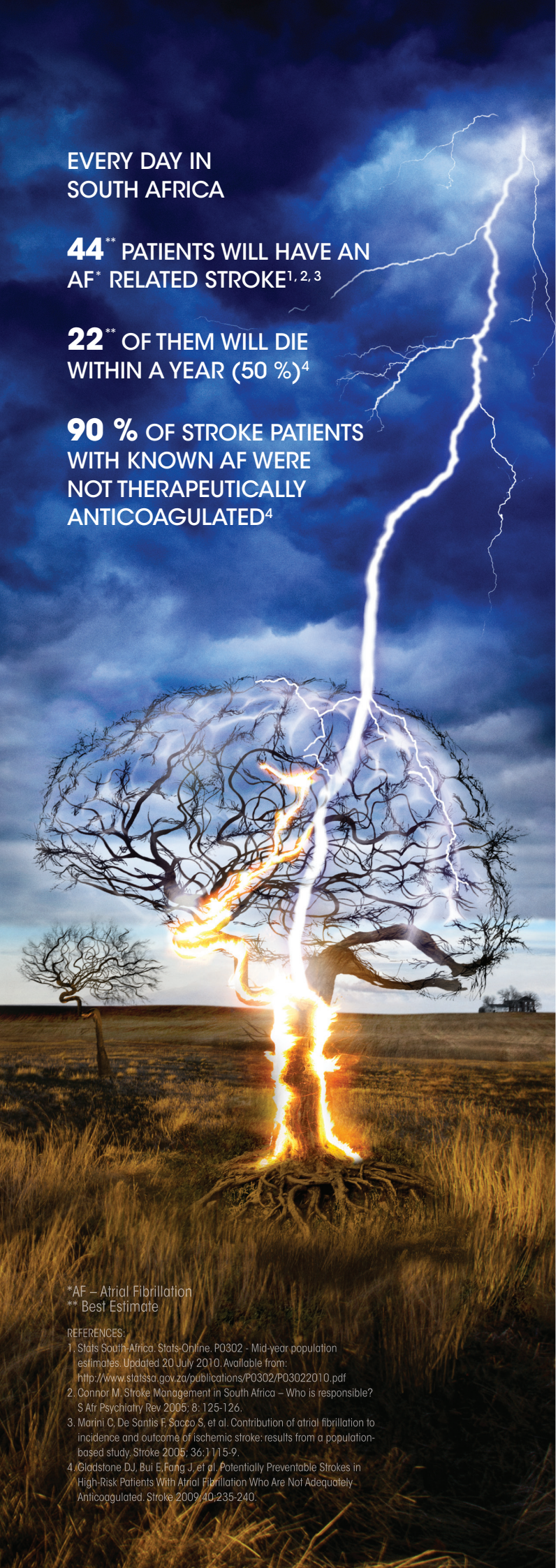

THINGS ARE ABOUT TO CHANGE IN ANTICOAGULATION THERAPY

Boehringer Ingelheim

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BI Ref No. 254/2010 (Nov 10)

Stroke prevention in atrial fibrillation

Prof Michael Ezekowitz, Thomas Jefferson Medical School, Wynnewood, Pennsylvania, USA

When it comes to the prevention of thrombo-embolism, the entire picture is changing, thanks to the advent of new agents such as the direct thrombin inhibitors, notably dabigatran. 'They are going to have a huge impact and in future we will see less use of warfarin and antiplatelet agents such as aspirin and clopidogrel', says Prof Michael Ezekowitz. He was in South Africa recently at the invitation of Boehringer Ingelheim.

Dabigatran is the first of these novel agents to be approved and Prof Ezekowitz was one of the principal investigators in the RE-LY study, which evaluated its efficacy and safety relative to warfarin.

It is a common consensus that anticoagulation in atrial fibrillation is the most preventive measure in cardiovascular medicine. Various studies have shown consistently that warfarin reduces stroke by around 75% in these patients. 'And yet physicians' prescribing habits are often more influenced by anticoagulation's risks, such as intracerebral bleeding, rather than its benefits', continues Prof Ezekowitz. 'It is well known that if a physician encounters an anticoagulation-related adverse event, he/she is much less likely to prescribe warfarin again in the next six months.'

The RE-LY trial compared dabigatran to warfarin and one of its key findings was a dramatic reduction in intracerebral bleeding with the novel agent. 'The trial was very successful and the challenge we face now is to translate its results into clinical practice. It's therefore important to understand the pharmacology of dabigatran so that we can match each clinical situation with the drug, thus ensuring the best decision.'

The prodrug dabigatran etexilate is converted completely to active dabigatran, ensuring that patients are therapeutically anticoagulated within an hour. It is noteworthy that the P450 system, which accounts for much of warfarin's variability, is not involved here.

Dabigatran reaches peak plasma concentration at two hours. 'It's a twice-daily oral treatment that needs to be taken in the morning with breakfast and in the evening with dinner', observes Prof Ezekowitz. 'We as physicians need to make patients aware of their responsibility to be compliant.'

In a study population of over 18 000 patients, dabigatran was shown to be highly predictable and no monitoring is required. Drug–drug interactions are few and only rifampin is contraindicated, as it increases the clearance of dabigatran, resulting in sub-therapeutic levels.

'Because 80% of dabigatran is eliminated by the kidneys, it is important to know patients' renal status before prescribing.' Prof Ezekowitz underscores that this requires measurement of creatinine clearance, and not just serum creatinine. 'Dabigatran should only be used when the creatinine clearance is above 30 ml/min', he says.

The RE-LY study

The trial evaluated two doses of dabigatran (110 and 150 mg) against warfarin, and its primary objective was to show non-inferiority of the new agent. 'A major achievement was getting the dose right to ensure the optimal antithrombotic effect with minimal bleeding', says Prof Ezekowitz.

Fifty per cent of patients were warfarin naïve as this allowed for a fairer comparison of the two treatments. Those on established warfarin treatment were potentially biased by their having been shown to be able to tolerate warfarin over time.

The trial produced some surprising findings. 'While the 110-mg dose achieved the objective of being non-inferior to warfarin, the 150-mg dose was shown to be superior to warfarin by 35%. This efficacy was an extremely consistent finding. Both doses were also shown to be safer than warfarin in respect of life-threatening bleeds – 33% for the lower dose and 20% for the higher dose of dabigatran.'

Another unexpected outcome occurred in respect of haemorrhagic stroke. 'While we're not yet sure of the mechanism via which this occurs, both doses of dabigatran reduced the incidence of haemorrhagic stroke dramatically. This finding was highly statistically significant and consistent across all subgroups. This has very important implications for our prescribing practice, which is currently driven by fear of haemorrhage. We need a change of mindset, as with dabigatran we can actually prevent a large number of events.'

All-cause and vascular mortality were significantly reduced with the 150-mg dose, while the 110-mg dose achieved non-inferiority. The US Food and Drug Administration have therefore approved the twice-daily 150-mg dose as the optimal one. Prof Ezekowitz believes, however, that there are patients for whom the 110-mg formulation is the better choice, notably those at high risk of stroke and systemic embolism. These data have yet to be published, however.

Prof Ezekowitz cautions nonetheless that dabigatran is not a perfect drug. Both doses were associated with a higher occurrence of dyspepsia than warfarin, as well as a greater likelihood of gastrointestinal bleeding. That said that these adverse events appeared to be more likely in elderly individuals with compromised renal function. Major gastrointestinal bleeding was more common in patients over 75 years old, making the case that the lower dose might also be preferable in these patients.

In summary, Prof Ezekowitz emphasised that 'the 150-mg dose is superior or at least non-inferior across all efficacy and safety outcomes, with the exception of major gastrointestinal bleeding, and the 110-mg dose of dabigatran is non-inferior to well-controlled warfarin in terms of efficacy, and superior in terms of safety.'

He concluded that when looking at the control of warfarin, if you analysed the results for different times in the therapeutic range, dabigatran was superior to poorly controlled warfarin across every parameter.

P Wagenaar, Gauteng correspondent

Stroke risk reduction: focus of the new ESC guidelines

$CHADS_2$ risk scoring is an easy off-top-of-the-head method to measure stroke risk in atrial fibrillation (AF) patients, but misses true predictive value and should be replaced by CHADS plus vascular risk (CHA_2DS_2-VASC). This expansion to the CHADS risk score is advocated in the new expert ESC guidelines for the management of atrial fibrillation.[1]

Atrial fibrillation is the commonest cardiac arrhythmia, occurring in 1–2% of the general population, with its prevalence set to double as populations age. This arrhythmia is responsible for one in five strokes worldwide and is of particular concern because AF-associated strokes are often fatal, with surviving stroke patients left more disabled by their stroke, and also facing an increased likelihood of suffering a further stroke.

This vulnerability results in increased costs of care for AF-related stroke, some 50% higher than non-AF-related stroke. Atrial flutter carries a similar risk of stroke and in these patients stroke-risk prediction is very important.

The $CHADS_2$ risk score was developed in the early 2000s and was initiated by the AF investigators and Stroke Prevention in Atrial Fibrillation (SPAF) investigators.[2] In this point system, stroke/TIA is awarded two points, and one point each for year above 75 years, hypertension, diabetes or recent cardiac failure. The adjusted stroke rate was determined from data based on a cohort of hospitalised AF patients. This score is now well established and forms an ideal base for the more predictive CHA_2DS_2-VASC score (Table 1).

Using the new CHA_2DS_2-VASC score, effective vitamin K antagonist (VKA) anti-coagulation treatment within INR targets of 2 to 3 is recommended for patients with AF with a score of 1 and higher, provided there are no contra-indications and with appreciation of the patient's values and perceptions.

The guidelines note that there is no place for aspirin therapy in AF-related stroke prevention, except perhaps in younger women under the age of 65 years with no other risk factors than AF. This view was mainly based on the magnitude of stroke reduction from aspirin versus placebo, which showed a non-significant 19% benefit of aspirin over placebo in AF-related stroke.[3]

In the ACTIVE-W trial,[4] warfarin was shown to be superior to the combination of clopidogrel plus aspirin, with no difference in bleeding events between treatment arms. In fact, the ESC guidelines suggest that, based on this trial, which mainly recruited patients who physicians regarded as being unsuitable for VKA therapy, the combination of aspirin and clopidogrel could perhaps be best seen as an interim measure where VKA is unsuitable, rather than an alternative to VKA in patients at high bleeding risk.

Direct comparisons have also been made between VKA and aspirin in stroke prevention, showing significant superiority of warfarin to aspirin, with a relative risk reduction of 39%; and no difference in the risk of major haemorrhage between warfarin and aspirin.[5] While the ESC guidelines refer only briefly to new investigational agents, they note the importance of the RE-LY study on the oral, direct thrombin inhibitor, dabigatran etexilate.[1]

In the RE-LY (Randomised Evaluation of Long-term anticoagulant therapY with dabigatran etexilate) study, dabigatran 110 mg b.i.d. was shown to be non-inferior to VKA for the prevention of stroke and systemic embolism, with lower rates of major bleeding. Dabigatran 150 mg b.i.d. however was associated with lower rates of stroke and systemic embolism with similar rates of major haemorrhage, compared with VKA.[6]

With the recent FDA approval of dabigatran for stroke reduction in AF, this anticoagulant has a significant role to play in the arena of stroke prevention in AF.

J Aalbers, Special Assignments Editor

TABLE. 1 CHA_2DS_2-VASC SCORE AND STROKE RATE[1]

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF

'Major' risk factors	*'Clinically relevant non-major' risk factors*
Previous stroke, TIA, or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤ 40%) Hypertension, diabetes mellitus female gender, age 65–70 years vascular disease

(b) Risk factor-based approach expressed as a points-based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1 or 2 points)

Risk factor	*Score*
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease	1
Age 65–74 years	1
Gender category (i.e. female)	1
Maximum score	9

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	*Patients (n = 7 329)*	*Adjusted stroke rate (%/year)*
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

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Prasugrel offers consistent platelet control in appropriate patients requiring treatment

Lilly launches prasugrel (Efient) in South Africa

Prasugrel represents a major breakthrough in anti-platelet therapy for patients with acute myocardial infarction (AMI), offering significant benefits over the past decade's mainstay therapy of clopidogrel and aspirin in percutaneous coronary interventions (PCI).

'In simple, practical terms, prasugrel is good at stopping re-occlusion and stent thrombosis' – *Dr Tony Dalby, Johannesburg*

Supporting his view, Prof Jean-Pierre Bassand of the University of Besancon, France, described the development of prasugrel, which is a third-generation thienopyridine and a powerful inhibitor of ADP-induced platelet aggregation (IPA).

'The defining difference between prasugrel and clopidogrel is that prasugrel provides more consistent inhibition and a faster onset of action, achieving 70 to 80% inhibition of platelet activity within one hour compared to clopidogrel', Dr Bassand noted.

The active metabolites of prasugrel and clopidogrel are virtually identical regarding liver metabolism; but clopidogrel requires a two-step process, which includes a cytochrome P450-dependent process. This has resulted in less anti-platelet function and lower levels of the active metabolite in patients with defined genetic polymorphisms. Also, considerable opportunity exists for drug interactions with clopidogrel, leading to excessive levels of clopidogrel and an increased hazard of bleeding.

In the development of prasugrel, the double-blind phase II trial (JUMBO) in acute coronary syndromes (ACS) defined the most effective dose of prasugrel as a 60-mg daily loading dose, followed by a 10-mg maintenance dose, with the least incurred hazard of bleeding in PCI patients, compared to clopidogrel.[1]

'Switching from clopidogrel to prasugrel is possible, with improved platelet inhibition without additional risk. However, switching from prasugrel to clopidogrel reduces effective inhibition of platelet aggregation and may increase thrombotic and ischaemic risk' – *Prof Jean-Pierre Bassand*

The primary end-point of the trial was the prevalence of clinically significant (TIMI major plus minor) non-CABG-related bleeding events in prasugrel- versus clopidogrel-treated patients. Haemorrhage complications were infrequent with no significant bleeding differences between prasugrel- and clopidogrel-treated patients in this trial.

'The TRITON-TIMI-38 trial followed and was a very large trial of patients with acute coronary syndromes, undertaken to prevent thrombotic complications of scheduled PCI. It must be emphasised that this was a PCI trial with all the typical complications of this procedure', Dr Bassand stressed.[2]

South Africa participated in this study, submitting some 400 patients of the total of 13 600 patients recruited in the trial. Patients were randomly assigned to receive prasugrel (60-mg loading and a 10-mg maintenance dose) or clopidogrel (300-mg loading and 75-mg maintenance dose).

'It is important to stress the timing of the prasugrel intervention. After the anatomy was known, a loading dose was given before PCI in only a quarter of the patients; 75% received the therapy during PCI or later', remarked Dr Bassand.

The efficacy of prasugrel was clear, with a 19% relative risk reduction (RRR) in cardiovascular death, myocardial infarction (MI) and stroke at a year or more (450 days), compared to clopidogrel. This benefit was largely driven by the reduction in all forms of MI.

Timing of prasugrel administration in ACS

- Primary PCI – at presentation
- Stent thrombosis – at presentation
- Diabetic patients – at time of PCI

'The benefit of prasugrel over clopidogrel occurred very early, in the first three days following PCI', Dr Bassand noted, 'and the curves continued to diverge over time. Benefits in the reduction of stent thrombosis (absolute risk reduction 2.4 vs 1.1%, relative risk reduction 52%) was also significant in this population of mainly NSTEMI (unstable angina/non-ST-segment elevation myocardial infarction) and STEMI patients.' There was an increased risk of major bleeding, including fatal bleeding with prasugrel over clopidogrel but overall mortality did not differ significantly between the treatment groups.

'In patients weighing less than 60 kg, prasugrel, in my view, is not completely contra-indicated. A maintenance dose of 5 mg could be given based on pharmacokinetic studies' – *Dr Lev*

'Some patients, the STEMI patients and the diabetic patients with acute coronary syndromes, derived more benefit from prasugrel. Further evidence has highlighted these patients as being the most suitable for prasugrel intervention as they show benefits without the increased major bleeding in the larger TRITON-TIMI group', Dr Bassand stressed.[3,4]

'Prasugrel treatment is clearly to be favoured above clopidogrel in STEMI patients. In diabetic patients of which there were 3 146 in TRITON-TIME 38, there was a 30% RRR without any excess of bleeds and no major CABG bleeds.'

'There were some patients in whom the powerful prasugrel anti-platelet effect was accompanied with a higher bleeding risk. Clopidogrel was better in patients with prior stroke/TIA, in patients over the age of 75 years and in patients with a low body weight, below 60 kg. In the older patient over 75 years without co-morbidities, you can however, still consider the use of prasugrel', Dr Bassand noted

The increase in spontaneous bleeding, which is the major category of prasugrel-induced bleeding, is dominated by gastrointestinal bleeds, and the use of proton pump inhibitors (PPI) is advocated in the maintenance period of prasugrel use.

Prasugrel addresses gaps in clopidogrel efficacy in acute coronary syndromes

'While clopidogrel is an excellent drug that has changed the landscape of cardiology by enabling PCI and reducing thrombotic complications, its efficacy

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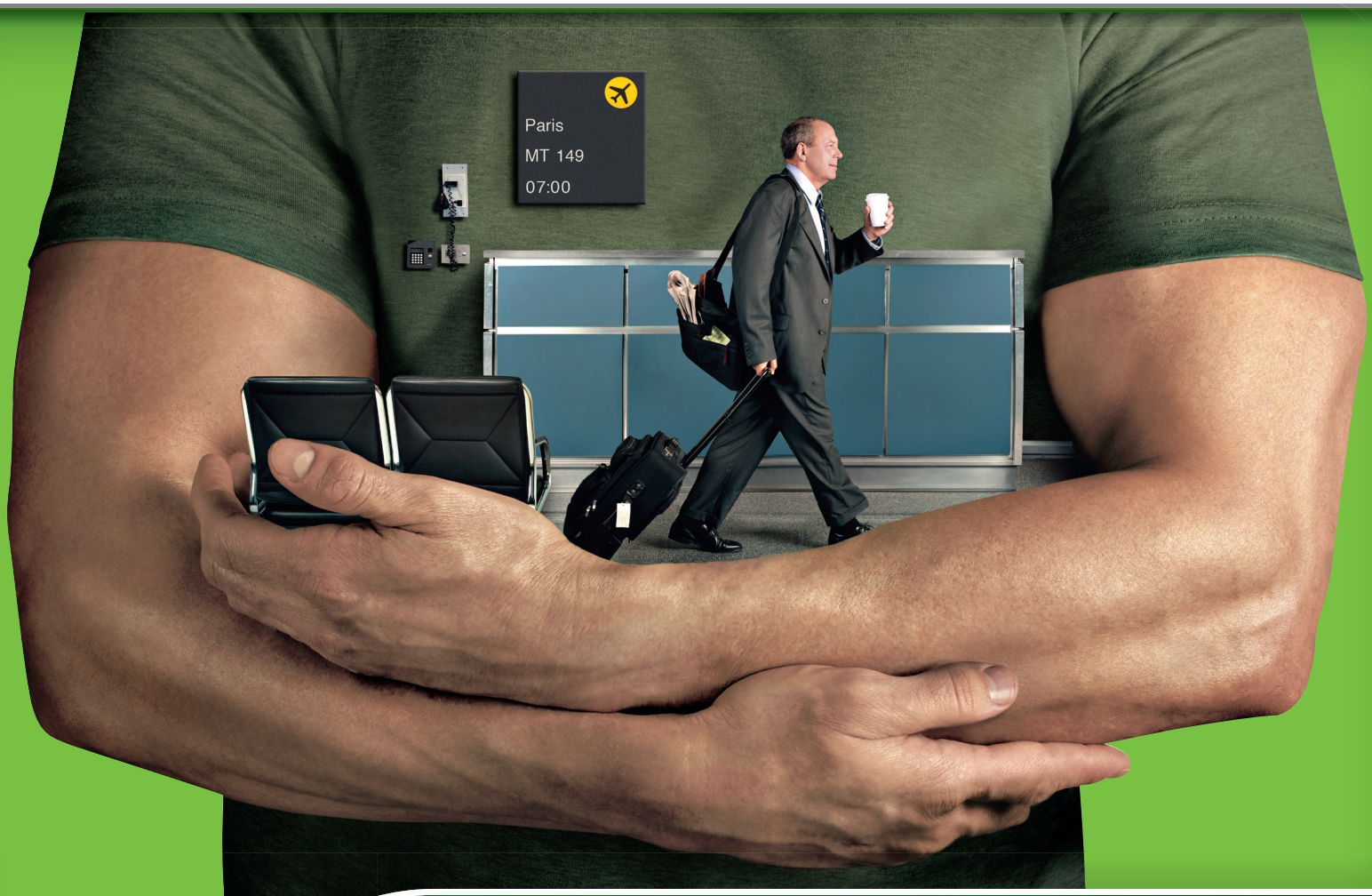

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Surgery in the face of prasugrel pre-treatment

In patients on prasugrel, as for clopidogrel, surgery should be delayed for at least seven days. If the CABG/surgery cannot wait, platelet transfusion is necessary. Platelet function tests can also add useful information on risk of bleeds.

is hampered by its wide variability in platelet inhibition, with consequent risk of stent thrombosis and MI in poor-responders, and its slow onset of action, which is particularly relevant to PCI in STEMI patients.' Dr Eli Lev, director of the Cardiac Catheterisation Laboratory, Petah-Tikva, Israel, an active researcher in the field of platelets and anti-coagulation, presented this view at the Lilly-sponsored symposium held in Cape Town recently.

The main reason for the variability of the clopidogrel response lies in its complex metabolism from pro-drug to active metabolite and the many enzymes that can be affected. It has been shown that 30% of Caucasians are carriers of the CYP^2C^{19} reduced-function allele, which results in low metabolism of clopidogrel to the active metabolite.

Numerous studies and meta-analyses have shown that being a low/non-responder to clopidogrel is a significant risk factor for suffering a catastrophic event. A study by Buonamici *et al*. on the effects of non-response to clopidogrel in patients receiving drug-eluting stents showed a very significant increase in the incidence of stent thrombosis of 8.6% in non-responders compared to 2.3% in responders.[5] The overall rate of stent thrombosis was 3.1% over the six-month period of this prospective study in an American academic hospital.

Various meta-analyses have shown a three to four-fold increase in stent thrombosis in clopidogrel low responders and a moderate but significant increase in mortality.

In a Xhosa population, unique genetic profiles with novel CYP^2C^{19} allelles have been found which can influence clopidogrel responses.[6] 'This is certainly an interesting field which warrants further research', Dr Lev noted.

Prasugrel's metabolism is much more efficient and studies have shown that carriers of the clopidogrel reduced-function CYP^2C^{19} alleles do not show altered metabolism of prasugrel, nor are prasugrel's platelet aggregation or cardiovascular event rates affected.[7] 'This is because prasugrel's metabolism is only a one-step process with little opportunity for the genetic make-up of the patient to influence prasugrel's anti-platelet action. Even patients who are non-responders to clopidogrel are responsive to prasugrel', Dr Lev noted.

Efforts to increase platelet inhibition by increasing the clopidogrel dose to higher than the approved levels of 600 mg loading dose and 150 mg daily maintenance dose have been compared to the standard prasugrel therapy in patients undergoing cardiac catherterisation for planned PCI.[8] This PRINCIPLE-TIMI 44 study showed that the 60-mg prasugrel loading dose and 10-mg maintenance dose resulted in a greater anti-platelet effect, which was consistent with that of the high clopidogrel treatment.

Implications of TRITON-TIMI 38 for the interventionist

You can count on Efient

'The importance of the TRITON-TIMI 38 trial is also its very effective prevention of stent thrombosis regardless of the type of intracoronary stent used', Dr Lev stressed.[9] Ninety-six per cent of the patients (12 844) in TRITON-TIMI 38 received at least one coronary stent, with approximately equal distribution of drug-eluting and bare-metal stents.

'Stent thrombosis is "the perfect platelet storm" with very catastrophic consequences and a 20 to 30% mortality rate, even though it is a relatively rare occurrence (1% of patients)', Dr Lev noted. 'Prasugrel invites the use of personalised and tailored medicine where the clinician should risk-stratify his patient to optimise anti-platelet therapy', Dr Bassand and Dr Lev concluded.

J Aalbers, Special Assignments Editor

Key take-home messages

- Prasugrel has been shown to be an effective inhibitor of platelet aggregation.
- The FDA has approved prasugrel.
- Prasugrel significantly reduces ischaemic events.
- It has an especially marked reduction in stent thrombosis.
- It has stronger benefits in patients with STEMI, stent thrombosis and diabetes.

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Substantial evidence for colorectal cancer reduction with daily low-dose aspirin

High-dose aspirin (≥ 500 mg daily) taken for a period of five years has been shown in long-term follow-up studies to reduce the risk of colorectal cancer in the next decades of the patient's life. However, the greater risk of bleeding complications at this high dose reduces aspirin's potential in primary prevention of cancers.

New data from four trials of aspirin,[1] using daily dosages from 75 to 300 mg were compared to the high-dose aspirin studies and showed:

- 75 mg aspirin taken daily is as effective as high-dose aspirin in reducing the 20-year incidence of colorectal cancer (by 30%) if taken for approximately five years.
- Not only did the lower dose of aspirin reduce the incidence of these cancers, it also reduced mortality from colorectal cancer.
- The reduction in fatal colorectal cancer tended to be greater than the reduction in incidence.
- Very low daily doses of aspirin tended to not be effective in the prevention of colorectal cancer.
- The reductions in both incidence and death due to colorectal cancer were greater for proximal cancer tumours than distal colon or rectal tumours.
- The reduction in 20-year risk of death due to colorectal cancer was larger than expected.
- Larger doses, above 300 to 1 200 mg daily, did not confer any additional benefits in terms of reduced incidence or deaths from colorectal cancer.

The long-term absolute risk reduction of 1–5% after long-term, low-dose aspirin treatment has implications for clinical practice. It adds to the primary preventative benefits of aspirin and may tip the balance in favour of aspirin compared to newer anti-platelet agents.[2]

J Aalbers, Special Assignments Editor

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References are available on request

Lilly launches Efient

Lilly SA, Pty (Ltd) is proud to announce the launch of Efient (prasugrel). Efient is a new oral thienopyridine. Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the reduction of atherothrombotic events in patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI) as follows:

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