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Editorial

The Pan-African Society of Cardiology (PASCAR) in 2013 and beyond

ANASTASE DZUDIE, BONGANI M MAYOSI

Abstract

The biennial Congress of the Pan-African Society of Cardiology (PASCAR) was held in Dakar from 16 to 19 May 2013 under the patronage of his Excellency, Macky Sall, president of the Republic of Senegal. This meeting was remarkable in the diversity of its 700 participants from English-, French- and Portuguese-speaking Africa. Important aspects of cardiovascular disease in Africa were presented in 195 abstracts and numerous talks; the topics were hypertension, obesity, diabetes, heart failure, cardiomyopathies, coronary heart disease, stroke and rheumatic heart disease. The general assembly meeting was marked by the review and adoption of a new constitution and elections of a new PASCAR governing council that will be in office for the next four years. The new leadership of PASCAR has committed itself to strengthening the administrative infrastructure of the organisation, developing programmes to address education and training needs of African cardiovascular practitioners, developing a pan-African multi-national research platform, and ensuring that ministries of health implement national programmes for the prevention and control of cardiovascular and other non-communicable diseases.

PASCAR board members. Back row, from left to right: Dr Anastase Dzudie, Cameroon, assistant general secretary (Central Africa); Dr Harun Otieno, Kenya, assistant general secretary (East); Dr Saad Subahi, Sudan, vice-president (North); Prof Elijah Ogola, Kenya, vice-president (East); Dr Awad Mohamed, Sudan, assistant general secretary (North); Prof BA Serigne, Senegal, vice-president (West); Prof Samuel Kingue, Cameroon, vice-president (Central); Prof Johan Brink, South Africa, assistant general secretary (South). Front row from left to right: Prof Toure Ali Ibrahim, Niger, assistant general secretary (West); Dr Ana-Olga Mocumbi, Mozambique, vice-president (South); Prof Bongani Mayosi, South Africa, president; Prof Karen Sliwa-Hahnle, South Africa, treasurer; Dr Benedict Anisiuba, Nigeria, secretary general.

Introduction

Since its conception by a small group of African cardiologists during the late 1970s, the Pan-African Society of Cardiology (PASCAR) has undergone three phases. These include an early growth spurt, characterised by regular continental meetings from 1981 to 1997; a period of stagnation from 1998 to 2003, during which no PASCAR meetings were held; and the renaissance phase that started in Accra, Ghana in October 2004 at a conference that was attended by 40 delegates, mainly from Cameroon, Ghana, Nigeria and South Africa.[1] Since Ghana, PASCAR has been gaining momentum in its work of galvanising health practitioners in Africa to improve clinical care and prevention of cardiovascular disease.

In 2007, the 8th PASCAR congress held in Nairobi, Kenya attracted over 300 participants from countries in all regions of Africa and beyond. A similarly global audience attended the 9th PASCAR congress in Abuja, Nigeria in September 2009, while the 10th congress two years later in Kampala, Uganda attracted about 400 global participants, mainly from English-speaking Africa. The achievement of the 2013 Dakar meeting was to bring together English-, French- and Portuguese-speaking Africans and foster understanding between these historically separated groups.

Opening ceremony

The PASCAR congress was held in Dakar from Wednesday 15 to Sunday 19 May 2013 under the patronage of his Excellency Macky Sall, president of the Republic of Senegal. At the opening ceremony, one minute of silence was observed in honour of the three distinguished members of PASCAR who have passed away since the previous meeting (the late President of PASCAR, Prof Oluwole Adebo of Nigeria, the late Editor-in-Chief of the *Cardiovascular Journal of Africa*, Prof Andries Brink of South Africa, and Prof Ndobo Pierre from Cameroon).

Prof Walinjon Muna, a past president of PASCAR, gave the opening address on the burden of cardiovascular diseases (CVD) in Africa and how to define specific strategies to control this rising burden of disease. He was followed by Prof Abdou Ba, president of the organising committee, who expressed his gratitude to all contributors, with particular credit to the highest Senegalese authority for understanding the concerns of heart specialists and joining PASCAR in his fight against CVD.

Prof Samuel Omokhodion, the then secretary-general, recalled the hard work of PASCAR's founders and subsequent leaders through a brief history, and their merits for having created an organisation such as PASCAR, which has been integral to

improving the cardiovascular health of the people of Africa over the last three decades, despite a difficult socio-economic and political context. The secretary-general also expanded on the challenges that the present and future generations face to carry on the charge of furthering the health of Africans.

President Macky Sall expressed his gratitude to the organisers of the meeting for having solicited him and said he was proud to be in the 'heart of heart specialists'. He was fully convinced and would advocate everywhere that Africa must build protections against heart disease so as to stop hypertension and other cardiac risk factors from becoming established epidemics on the continent. He welcomed all the PASCAR delegates to Senegal, a welcome worthy of the legendary Senegalese 'teranga' (the Wolof word for hospitality is 'teranga' and it is so identified with the pride of Senegal that the national football team is known as the Lions of Teranga). About 700 delegates from English-, French- and Portuguese-speaking African countries and also from Europe and the USA attended the Dakar meeting.

Workshops

Five workshops ocurred simultaneously on Wednesday morning and were very well attended. The workshop on interventional cardiology was hosted by the Pan-African Course on Interventional Cardiology (PAFCIC), (represented by Prof Habib Gamra, Tunisia), PASCAR (represented by Prof Bongani Mayosi, South Africa) and the American College of Cardiology/ Association of Black Cardiologists (represented by Prof Ola Akinboboye, USA).

This workshop highlighted the growing incidence of ischaemic heart disease among Africans and the current difficulties in management, with very few acute cases benefiting from lytic therapy or primary coronary interventions. Some African countries such as Kenya have achieved significant progress in terms of acquiring invasive cardiac catheterisation laboratories, mainly in the private sector. Establishing a collaborative training and research programme between PAFCIC, PASCAR and ACC/ ABC will help increase the state of readiness of cardiovascular practitioners to cope with the rising burden of disease.

The echocardiography, rhythmology and paramedical workshops were very practical (hands-on training) sessions and were well attended by delegates.

Scientific sessions

Obesity, diabetes and hypertension

Dr Andre Pascal Kengne, a distinguished Cameroon researcher from the Medical Research Council, South Africa stated that evidence has been accumulating on the importance of the rising burden of diabetes mellitus and obesity on the African continent. This has been at an increasingly higher pace than previously expected and than elsewhere in the world. He showed important differences in prevalence across countries and between rural and urban regions.[2,3]

Prof Said Norou Diop (Senegal) stated that the care for diabetes largely remains suboptimal in most countries, which are not adequately prepared to face the prevention and control of diabetes. The costs of caring for the condition pose a tremendous challenge to most local economies. Prof Jean Jacques Monsuez (France) described the higher prevalence of CVD among diabetic patients.

Prof Terrence Forester (Jamaica) showed that nutrition in early life influences the pathogenesis and prevention of cardiometabolic disease in Africans. The panel concluded that research is needed to contextualise the existing evidence for diabetes screening and prevention in African settings, and to better characterise the interaction of genetic and environmental factors on the occurrence of diabetes and obesity on the continent.

The rising incidence of obesity and diabetes in Africa parallels the incidence of hypertension. Prof Moustapha Saar (Senegal) presented hypertension as the dominant risk factor for CVD in Africa, with a prevalence ranging from 20 to 35% of the adult population, and this prevalence is anticipated to rise dramatically. Dr Daniel Lemogoum (Cameroon) said hypertension is currently poorly diagnosed, poorly treated and poorly controlled in Africa, exposing the African continent to the burden of serious adverse outcomes. He concluded that an updated but simplified Pan-African guideline for management of this disease is needed.[4]

Prof Jean Jacques Blacher (France) presented the current French and also European guidelines for treatment of hypertension. He insisted on the use of the triad combination of a diuretic, an inhibitor of the renin angiotensin aldosterone system and a calcium channel blocker whenever necessary to control resistant hypertension. The panel concluded that decisive actions are needed by African governments and policymakers to stop the negative health effects of uncontrolled hypertension.

Stroke

Prof Mouhamadou Mansour Ndiaye (Senegal) gave an overview of the epidemiology and diagnosis of stroke. According to him, the burden of cerebrovascular disease manifests mainly as stroke caused by high blood pressure, and is now an established important cause of premature disability, morbidity and mortality in most regions of the continent.

Prof Ibrahima Diakhaté (Senegal) advocated for the increased availability of non-invasive imaging of stroke in most African centres. Prof Albertino Damasceno (Mozambique) presented the management strategies of stroke, which need to be effected through concerted implementation of several public health measures, primary and secondary prevention policies and cost-effective treatment, running in parallel with and underpinned by coordinated research initiatives.[5]

Heart failure and cardiomyopathies

The results of THESUS-HF, the African prospective registry of heart failure, which were published in 2012, were presented by Prof Albertino Damasceno (Mozambique).[6] This study has provided several key insights into the epidemiology and prognosis of acute heart failure and cardiomyopathy on the continent, with hypertension emerging as the leading risk factor for heart failure, highlighting once more the need to place the treatment and control of hypertension in a central role for the global improvement of cardiovascular health in Africans.

Prof Abdoul Kane (Senegal) gave a comprehensive lecture on heart failure with preserved ejection fraction, with emphasis on new approaches to diagnosing the disease. Prof Karen Sliwa (South Africa) demonstrated that peripartum cardiomyopathy (PPCM) is one of the prevalent aetiologies of heart failure in women and is associated with adverse outcomes. She stated that the discovery of potential mechanistic pathways for

cardiomyopathy is raising the promise of new interventions, such as the proposed role of bromocriptine in the treatment of this disease.[7] Prof Jean Claude Daubert (France) gave a historical perspective of cardiac resynchronisation therapy for heart failure, with reference to its feasibility in Africa.

Oral communications, posters and symposia

The Dakar meeting topped the number of abstracts ever submitted to a PASCAR meeting, with 48 oral communications and 147 posters presented. Three symposia were organised by pharmaceutical companies.

Multicentric and collaborative research projects

Preliminary results of multicentric collaborative research projects being conducted on the continent were presented. Drs Friedrich Thienneman and Anastase Dzudie presented the Pan-African PUlmonary hypertension COhort study (PAPUCO) platform, which was launched at the PASCAR meeting in May 2011 in Kampala, Uganda. The study has recruited 132 patients with pulmonary hypertension. It is aimed to complete the recruitment of 200 patients with pulmonary hypertension by the end of August 2013, and six months of follow up will be completed by February 2014.

Dr Liesl Zuhlke (South Africa) presented preliminary results of the Global Rheumatic Heart Disease Registry (REMEDY),[8] followed by Prof Samuel Kingue (Cameroon) for the Valvafric study, a registry on rheumatic heart disease (RHD). Both registries concluded that RHD is still a major disease on the continent and associated with poor outcomes, especially in the absence of cardiac surgery.

Other sessions

The cardiac surgery and cardiac pacing sessions emphasised the need for training more specialised cardiologists and cardiac surgeons but also on the means to increase patient access to cardiac surgery and pacemakers. Sessions on vascular medicine as well as cardiac imaging were equally well attended and highlighted the low availability and affordability of other cardiac imaging, such as nuclear imaging, CT angiography and magnetic resonance imaging in African settings. Dr Ntobeko Ntusi from South Africa stated that while echocardiography will remain first line, other modalities do provide additional information, which affects management and henceforth will be made available in centres of excellence in Africa.

General assembly meeting

The meeting was held on 17 May and started at 17:40 with the vice president (West), Prof Abdou Ba presiding. The secretary-general, Prof Omokhodion circulated the working document for the constitutional review, the suggested amendments were discussed by the assembly, and the views of the congress were adopted.

Ten distinguished members were honored for the PASCAR Award, given their significant contributions in the foundation and/or growing of PASCAR. They were Prof Ayodele O Falase (Nigeria), Prof Olufemi Jaiyesimi (Nigeria), Prof Papa Koate (Senegal), Prof WFT Muna (Cameroon), Prof H Ojiambo (Kenya), Prof OM Pobee (Ghana), Prof JK Manuwelle (Zimbabwe), Prof HS Badawi (Egypt), Prof Hippolyte Agboton (Benin) and Prof Peter Omollo Odhiambo (Kenya).

A new executive was elected under the leadership of Prof Bongani M Mayosi, who then outlined four priorities for the society over the next four years: (1) to establish a strong administrative and financial base, (2) to satisfy individual needs of members, especially in the area of training, (3) to boost research on the continent so that Africa can gain respect in the world in the area of cardiovascular disease, and (4) to reach out to North African societies. He also stressed the need to ensure that ministries of health adopt and implement the '10 Best Buys' to combat heart disease, diabetes and stroke in Africa.[9] The success or failure of PASCAR will be judged on the extent to which these goals are achieved over the next four years.

Conclusion

This Dakar conference has once more confirmed the role of PASCAR as the premier umbrella association for national professional societies in cardiovascular medicine and surgery on the African continent. The election of a new and ambitious leadership demonstrated that PASCAR has turned the page of stagnation. It is now full of vitality and is poised to lead the continent, and be a leading force in area management of cardiovascular disease in the world during the third millennium.

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Cardiovascular Topics

Comparison of left atrial function in healthy individuals versus patients with non-ST-segment elevation myocardial infarction using two-dimensional speckle tracking echocardiography

ZHU JING, CHEN JIANCHANG, XU WEITING, GAO LAN, FARHAN SHAIKH, WU YANNI

Abstract

Left atrial (LA) function has been associated with adverse outcomes in patients after acute myocardial infarction. The purpose of the current study was to evaluate LA function in patients with non-ST-segment elevation myocardial infarction (NSTEMI) by two-dimensional speckle tracking echocardiography (2D STE). Fifty-one patients with NSTEMI and 40 age-matched normal control individuals were enrolled in this study. Conventional echocardiographic parameters and global longitudinal strain rate (GLSR) were measured at left ventricular (LV) and LA segments. Compared with healthy subjects, patients with NSTEMI had significantly increased LA volumes but significantly decreased LA emptying fraction and GLSR. LA-GLSR had significant correlations with the 2D Doppler echocardiographic parameters of LA function. In particular, global LA peak negative strain rate during early ventricular diastole (LA-GLSRe) was significantly correlated with both LA 2D Doppler echocardiographic parameters and LV contractile function. This could be suggested as a better indicator to evaluate LA function as a preferred parameter of STE.

Keywords: two-dimensional speckle tracking echocardiography, strain rate, non-ST-segment elevation myocardial infarction, left atrial function

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According to an authoritative survey, more than one million people die each year from coronary artery disease in China. Recently, impaired left atrial (LA) function and its detrimental effect on coronary artery disease has caused wide concern,[1] Left atrial function is one of the most important clinical parameters of two-dimensional speckle tracking echocardiography (2D STE), which is an innovative tool for more comprehensive and reliable echocardiographic evaluation of myocardial function.[2]

Compared with Doppler and 2D echocardiography, 2D STE has the advantages of angle independence, and is also less affected by reverberations, side lobes or drop-out artifacts. While this novel echocardiographic method has been frequently used to assess LV function,[3] it has more recently been used to evaluate atrial function in normal subjects and in conditions with atrial dysfunction.[4,5]

The aims of this study were to examine left atrial function using 2D STE in patients with non-ST-segment elevation myocardial infarction (NSTEMI) compared to healthy subjects and to define the feasibility of speckle tracking-based strain rate (SR) imaging for the evaluation of LA dysfunction after acute myocardial ischaemia.

Methods

Fifty-one patients (43 males and eight females; mean age 62.9 ± 11.1 years) were treated by percutaneous coronary intervention (PCI) for NSTEMI and were included in the study from December 2009 to November 2010, while 40 age-matched healthy subjects (35 males and five females; mean age 60.1 ± 9.8 years) with normal treadmill exercise stress echocardiography and no coronary risk factors were enrolled as a control group.

Patients with atrial fibrillation or flutter, valvular heart disease (of mild or greater severity), and poor left atrial images were excluded. The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University and a written informed consent was obtained from each participant.

Conventional 2D and Doppler echocardiography studies were performed using the Vivid7 Dimension ultrasound system (GE, USA) equipped with a 3S phased-array transducer (frequency range of 1.7–3.4 MHz). Echocardiographies of patients were performed 2.8 ± 0.6 days after NSTEMI. Cardiac dimensions were measured in accordance with recommendations of the American Society of Echocardiography.

M-mode echocardiography was used to measure LV end-diastolic and end-systolic diameters. LV ejection fraction (LVEF) was calculated from apical four- and two-chamber

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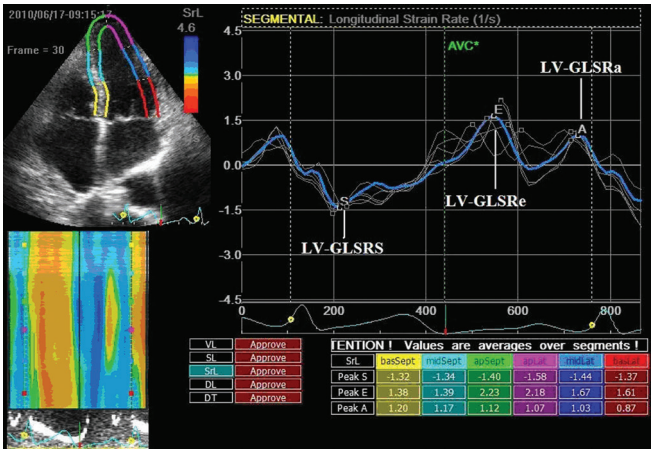

Fig. 1. Measurement of global longitudinal left ventricular strain rate from an apical four-chamber view. The dashed curve represents the global longitudinal ventricular strain along the cardiac cycle. LV-GLSRa = left ventricular global longitudinal peak late diastolic strain rate. LV-GLSRs = left ventricular global longitudinal peak systolic strain rate. LV-GLSRe = left ventricular global longitudinal peak early diastolic strain rate. AVC = aortic valve closure.

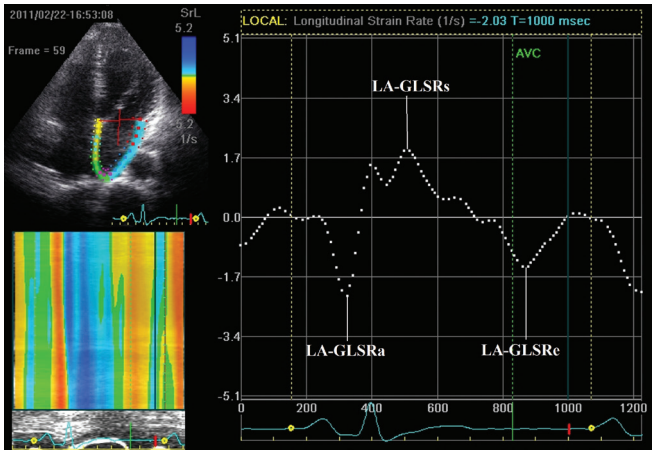

Fig. 2. Measurement of global longitudinal left atrial strain rate from an apical four-chamber view. The dashed curve represents the global longitudinal atrial strain along the cardiac cycle. GLSRa = left atrial global longitudinal peak negative strain rate during late ventricular diastole. GLSRs = left atrial global longitudinal peak positive strain rate during ventricular systole. GLSRe = left atrial global longitudinal peak negative strain rate during early ventricular diastole. AVC = aortic valve closure.

views, using the modified Simpson's rule. LA volumes were measured using the area–length method from apical four- and two-chamber views, according to the guidelines of the American Society of Echocardiography.[6]

Left atrial maximum volume (LAV_{max}) was measured at the end of LV systole, just before the opening of the mitral valve, LA minimum volume (LAV_{min}) was measured at the end of LV diastole, right after the closure of the mitral valve, and LA pre-atrial volume (LAV_p) was obtained from the diastolic frame before initial mitral valve re-opening elicited by atrial contraction. LA reservoir function was assessed using LA total EF = $(LAV_{max} - LAV_{min})/LAV_{max}$, LA conduit function was assessed using LA passive emptying fraction (LAPEF) = $(LAV_{max} - LAV_p)/LAV_{max}$, and LA booster pump function was assessed using LA active emptying fraction (LAAEF) = $(LAV_p - LAV_{min})/LAV_p$.

For 2D STE analysis, we obtained 2D gray-scale harmonic images in three apical planes (long axis of LV, four- and two-chamber). Three consecutive heart cycles were recorded and averaged. The frame rate was set between 60 and 90 frames per second.[7] Echocardiograms were digitally stored and later analysed off-line using acoustic-tracking software (Echo-Pac version 7.0, GE Vingmed).[8] A 16-segment LV model was obtained from the four- and two-chamber, and long-axis recordings.[9]

Two-dimensional strain software identified the endocardial border, and after tracing myocardial motion, was automatically tracked in each imaging view. Strain rate measurements from 16 segments were averaged to assess a LV global longitudinal parameter based on peak systole (LV-GLSRs), early diastole (LV-GLSRe), and late diastole (LV-GLSRa) (Fig. 1).

The LA myocardium was divided into six equidistant regions from apical four- and two-chamber views, while only three were analysed in the apical long-axis view because the remaining three in this view are part of the aortic valve and ascending aorta and not LA myocardium. The software generates strain rate curves for each atrial segment. Global strain and strain rate were also calculated by averaging values from 15 atrial segments. Lastly, we can get global LA peak positive strain rate during ventricular systole (LA-GLSRs), global LA peak negative strain rate during early ventricular diastole (LA-GLSRe) and global LA peak negative strain rate during late ventricular diastole (LA-GLSRa) (Fig. 2).

To assess inter- and intra-observer variabilities, variabilities in the measurements of LA-GLSRs, LA-GLSRe, LA-GLSRa, LV-GLSRs, LV-GLSRe and LV-GLSRa were evaluated in 20 subjects selected randomly. To assess the inter-observer variability, selected images were analysed by a second observer blinded to the values obtained by the first observer. To assess the intra-observer variability, selected images were analysed at a different time by an observer blinded to the results of the previous measurements.[10]

TABLE 1. CLINICAL FEATURES OF PATIENTS WITH NSTEMI AND THE CONTROLS

	Controls (n = *40*)	*NSTEMI* (n = *51*)	p-*value*
Age (years) (mean ± SD)	60.1 ± 9.8	62.9 ± 11.1	0.272
Male, *n* (%)	35 (87.5)	43 (84.3)	0.238
Female, *n* (%)	5 (12.5)	8 (15.7)	0.179
Height (cm)	167.06 ± 6.97	166.67 ± 7.30	0.546
Weight (kg)	61.56 ± 10.16	62.31 ± 9.70	0.626
Smoking	23	41	0.057
Body mass index (kg/m^2)	57.5	80.4	0.087
Hypertension (%)	1.69 ± 0.16	1.77 ± 0.15	0.001
Diabetes mellitus, *n* (%)	0	28 (54.9)**	0.001
Hyperlipidaemia, *n* (%)	0	12 (23.5)**	0.001
Occluded coronary artery, *n* (%)	0	26 (51.0)**	–
RCA, *n* (%)	–	2 (3.9)	–
LAD, *n* (%)	–	11 (21.6)	–
LCX, *n* (%)	–	8 (15.7)	–

RCA = right coronary artery, LAD = left anterior descending artery, LCX = left circumflex coronary artery. **$p < 0.01$.

TABLE 2. CONVENTIONAL 2D DOPPLER ECHOCARDIOGRAPHIC PARAMETERS IN PATIENTS WITH NSTEMI AND THE CONTROLS

	Controls (n = 40)	*NSTEMI (n = 51)*	p-*value*
LAV_{max} (ml)	45.33 ± 14.50	60.38 ± 17.64	0.001
LAV_{min} (ml)	16.18 ± 8.93	25.56 ± 12.59	0.001
LAV_{p} (ml)	27.32 ± 10.74	43.80 ± 16.59	0.001
LAPEF (%)	39.89 ± 13.65	28.96 ± 11.62	0.001
LAAEF (%)	42.74 ± 11.25	43.89 ± 11.67	0.637
LA total EF (%)	65.53 ± 10.20	59.06 ± 13.44	0.013
LVEF (%)	65.18 ± 5.22	58.08 ± 10.01	0.001

Date are expressed as mean ± SD.

TABLE 3. REPRODUCIBILITY OF LA AND LV GLOBAL STRAIN RATE

	Controls		*NSTEMI*	
	Intra-observer	*Inter-observer*	*Intra-observer*	*Inter-observer*
LA-GLSRs	0.94 (0.87–0.98)	0.95 (0.88–0.98)	0.95 (0.87–0.98)	0.98 (0.89–0.99)
LA-GLSRe	0.95 (0.88–0.98)	0.97 (0.91–0.99)	0.94 (0.87–0.98)	0.98 (0.90–0.99)
LA-GLSRa	0.94 (0.87–0.98)	0.96 (0.89–0.98)	0.94 (0.87–0.98)	0.93 (0.87–0.98)
LV-GLSRs	0.94 (0.87–0.98)	0.94 (0.85–0.97)	0.82 (0.76–0.96)	0.85 (0.67–0.94)
LV-GLSRe	0.95 (0.88–0.98)	0.94 (0.86–0.97)	0.93 (0.84–0.97)	0.92 (0.81–0.95)
LV-GLSRa	0.93 (0.84–0.97)	0.95 (0.88–0.97)	0.86 (0.80–0.98)	0.93 (0.85–0.97)

LA-GLSRs = LA global longitudinal peak positive strain rate during ventricular systole, LA-GLSRe = LA global longitudinal peak negative strain rate during early ventricular diastole, LA-GLSRa = LA global longitudinal and peak negative strain rate during late ventricular diastole, LV-GLSRs =LV global longitudinal peak systolic strain rate, LV-GLSRe = LV global longitudinal early diastolic strain rate, LV-GLSRa = LV global longitudinal late diastolic strain rate. Date are expressed as mean ± SD.

Statistical analysis

Data analysis was carried out using the statistical software package (SPSS, Rel 13.0, Chicago: SPSS Inc.). Continuous data were presented as mean ± SD. Differences between the NSTEMI and control groups were assessed by unpaired Student's *t*-test. Categorical parameters are presented as numbers (%), and were analysed using chi-square tests or Fisher's exact tests, as appropriate. For assessment of intra- and inter-observer variabilities, the Bland-Altman method was used.[11] The correlation between two variables was assessed using Spearman's rank correlation coefficient. A two-tailed *p*-value < 0.05 was considered significant for statistical inference.

Results

The main clinical features and 2D Doppler echocardiography data of the controls and NSTEMI patients are summarised in Tables 1 and 2, respectively. There were significant differences in clinical features, such as hypertension, diabetes and hyperlipidaemia between patients and healthy subjects. Patients with NSTEMI had significantly increased LAV_{max} (60.38 ± 17.64 vs 45.33 ± 14.50 ml, $p = 0.001$), LAV_{min} (25.56 ± 12.59 vs 16.18 ± 8.93 ml, $p = 0.001$), and LAV_{p} (43.80 ± 16.59 vs 27.32 ± 10.74 ml, $p = 0.001$), but significantly lower in LAPEF (28.96 ± 11.62 vs 39.89 ± 13.65%, $p = 0.001$), LA total EF (59.06 ± 13.44 vs 65.53 ± 10.20%, $p = 0.013$) and LVEF (58.08 ± 10.01 vs 65.18 ± 5.22%, $p = 0.001$).

The SR imaging of LA and LV was acceptable in all 40 healthy subjects, whereas four had one inadequately traced segment. The SR imaging of LA and LV was acceptable in 51 patients, whereas five had one inadequately traced segment. Twenty healthy subjects and 20 patients with NSTEMI were randomly selected for the assessment of intra- and inter-observer variabilities in the measurements of LA-GLSRs, LA-GLSRe, LA-GLSRa, LV-GLSRs, LV-GLSRe and LV-GLSRa, respectively.

Bland-Altman analysis of these parameters showed no evidence of any systematic difference regarding inter- and intra-observer variabilities. Table 3, and Figs 3 and 4 show the mean difference and confidence intervals of inter- and intra-observer variabilities.

Table 4 lists the SR imaging echocardiographic variables of the normal and NSTEMI groups. Compared with the controls, patients with NSTEMI had significantly decreased LA-GLSRs ($p = 0.001$), LA-GLSRe ($p = 0.001$), LV-GLSRs ($p = 0.004$), and LV-GLSRe ($p = 0.001$).

Correlations of LA-GLSRs, LA-GLSRe, LA-GLSRa, LV-GLSRs, LV-GLSRe and LV-GLSRa with parameters of LA volume and function in NSTEMI patients were performed (Table 5). LA-GLSRs showed modest correlations with parameters of LA volume and function, including LAV_{max} ($r = –0.610$, $p < 0.01$), LAV_{min} ($r = –0.668$, $p < 0.01$), LAV_{p} ($r = –0.638$, $p < 0.01$), LAPEF ($r = 0.376$, $p < 0.01$), LAAEF ($r = –0.303$, $p < 0.05$), LA total EF ($r = –0.412$, $p < 0.05$) and LVEF ($r = –0.334$, $p < 0.05$).

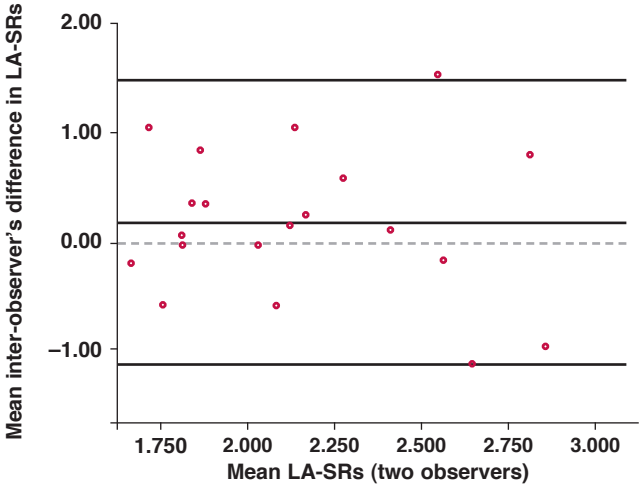

Fig. 3. Bland-Altman plots of inter-observer agreement for LA-GLSRs in patients with NSTEMI.

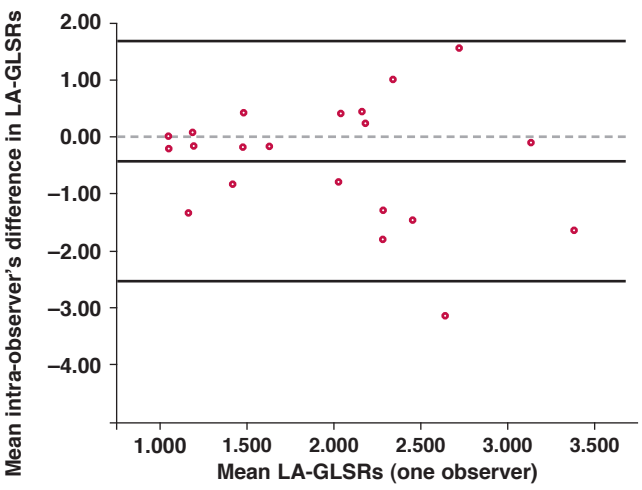

Fig. 4. Bland-Altman plots of intra-observer agreement for LA-GLSRs in patients with NSTEMI.

TABLE 4. 2D STE PARAMETERS IN PATIENTS WITH NSTEMI AND THE CONTROLS

	Controls (n =*36)*	*NSTEMI* (n = *46)*	p-*value*
LA-GLSRs	1.93 ± 0.48	1.59 ± 0.58	0.001
LA-GLSRe	–2.03 ± 0.70	–1.21 ± 0.52	0.001
LA-GLSRa	–2.25 ± 0.67	–1.90 ± 0.77	0.061
LV-GLSRs	–0.92 ± 0.19	–0.80 ± 0.22	0.004
LV-GLSRe	1.17 ± 0.38	0.78 ± 0.27	0.001
LV-GLSRa	0.71 ± 0.22	0.75 ± 0.21	0.062

LA-GLSRs = LA global longitudinal peak positive strain rate during ventricular systole, LA-GLSRe = LA global longitudinal peak negative strain rate during early ventricular diastole, LA-GLSRa= LA global longitudinal and peak negative strain rate during late ventricular diastole, LV-GLSRs = LV global longitudinal peak systolic strain rate, LV-GLSRe = LV global longitudinal early diastolic strain rate, LV-GLSRa = LV global longitudinal late diastolic strain rate. Date are expressed as mean ± SD.

TABLE 5. CORRELATION OF GLOBAL LA/LV STRAIN RATE PARAMETERS WITH LA VOLUME AND FUNCTION PARAMETERS IN PATIENTS WITH NSTEMI

Correlation	LAV_{max} *(ml)*	LAV_{min} *(ml)*	LAV_{p} *(ml)*	*LAPEF (%)*	*LAAEF (%)*	*LA total EF (%)*	*LVEF (%)*
LA-GLSRs	–0.610**	–0.668**	–0.638**	0.376**	–0.303*	–0.412*	–0.334*
LA-GLSRe	0.586**	0.530**	0.564**	–0.270	0.340*	0.256*	–0.477**
LA-GLSRa	0.604**	0.615**	0.590**	–0.298*	0.262	0.347	0.339
LV-GLSRs	–0.136	–0.165	–0.103	0.089	0.072	0.102	0.361*
LV-GLSRe	–0.062	–0.014	–0.022	–0.042	–0.030	–0.033	–0.414**
LV-GLSRa	0.162	0.203	0.199	–0.102	–0.067	–0.134	–0.405**

LA-GLSRs = LA global longitudinal peak positive strain rate during ventricular systole, LA-GLSRe = LA global longitudinal peak negative strain rate during early ventricular diastole, LA-GLSRa= LA global longitudinal and peak negative strain rate during late ventricular diastole, LV-GLSRs = LV global longitudinal peak systolic strain rate, LV-GLSRe = LV global longitudinal early diastolic strain rate, LV-GLSRa = LV global longitudinal late diastolic strain rate. Date are expressed as mean ± SD. *$p < 0.05$. **$p < 0.01$.

LA-GLSRe significantly correlated with LAV_{max} ($r = 0.586$, $p < 0.01$), LAV_{min} ($r = 0.530$, $p < 0.01$), LAV_{p} ($r = 0.564$, $p < 0.01$), LAAEF ($r = 0.340$, $p < 0.05$), LA total EF ($r = 0.256$, $p < 0.05$) and LVEF ($r = –0.477$, $p < 0.001$). LA-GLSRa had significant correlations with the following echocardiographic variables: LAV_{max} ($r = 0.604$, $p < 0.01$), LAV_{min} ($r = 0.615$, $p < 0.01$), LAV_{p} ($r = 0.590$, $p < 0.01$) and LAPEF ($r = –0.298$, $p < 0.05$).

LV SR parameters had no significant correlation with the following LA echocardiographic variables: LAV_{max}, LAV_{min}, LAV_{p}, LAPEF, LAAEF and LA total EF. In addition, LVEF was significantly correlated with LA-GLSRs ($r = –0.334$, $p < 0.05$) and LA-GLSRe ($r = –0.477$, $p < 0.001$) (Fig. 5), but not significantly correlated with LA-GLSRa ($r = 0.339$, $p > 0.05$).

LA-GLSRe correlated significantly with LV-GLSRe ($r = –0.644$, $p = 0.001$) (Fig. 6). However, both LA-GLSRs and LA-GLSRa showed no such significant correlation with LV-GLSRs (Fig. 7) and LV-GLSRa (Fig. 8), respectively.

Discussion

After several decades of investigation, current consensus recommendations state that LA function plays an important role in optimising overall cardiac function, and the changes in LA size and function are associated with cardiovascular disease and are risk factors for atrial fibrillation, stroke and death.[12–14] The left atrium serves as a blood reservoir during ventricular systole and a conduit for the passage of blood from the pulmonary veins into the left ventricle during early and middle ventricular diastole, as well as a booster pump increasing LV filling during late diastole.[15] In subjects with normal diastolic function, the relative contribution of the reservoir, conduit and pump function of the LA to the filling of the LV is approximately 40, 35 and 25%, respectively.[16]

Determined by conventional 2D echocardiography, LA function has been mainly evaluated using LA volumetric parameters and LA emptying fraction, such as LA total EF, LAPEF, and LAAEF, which may be used to evaluate the reservoir, conduit and booster pump components of LA function.[6,13] Parameters that evaluate LA function may have prognostic potential. LA reservoir function may predict the first atrial fibrillation or flutter episode in elderly subjects, and LA systolic force may predict cardiovascular events in a population with a high prevalence of hypertension and diabetes.[17,18]

However, all these echocardiographic parameters and others that evaluate LA function are influenced by LV dynamics and geometry and/or rely on measurements that are subjected to

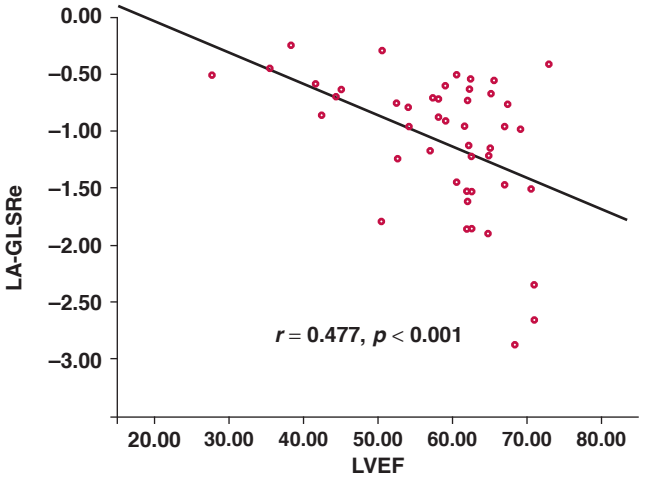

Fig. 5. Correlation between left ventricular ejection fraction (LVEF) and peak early diastolic strain rate of the left atrium (LA-GLSRe) in patients with NSTEMI.

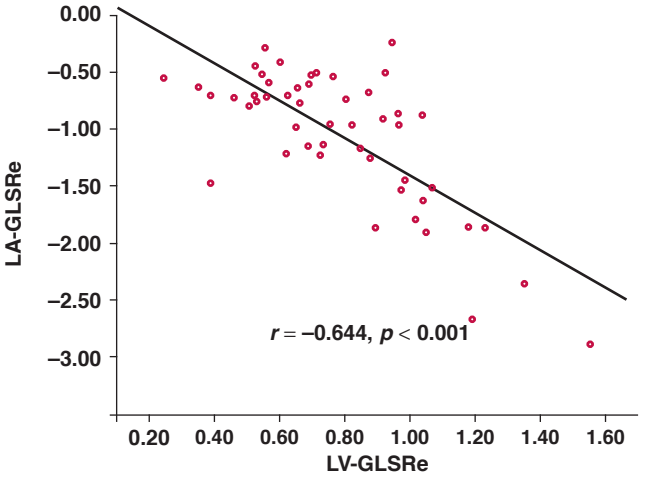

Fig. 6. Correlation between peak early diastolic strain rate of the left ventricle (LV-GLSRe) and peak early diastolic strain rate of the left atrium (LA-GLSRe) in patients with NSTEMI.

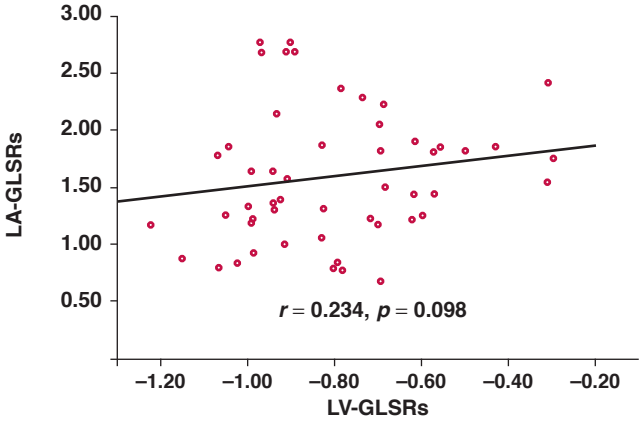

Fig. 7. Correlation between peak early diastolic strain rate of the left ventricle (LV-GLSRs) and peak early diastolic strain rate of the left atrium (LA-GLSRs) in patients with NSTEMI.

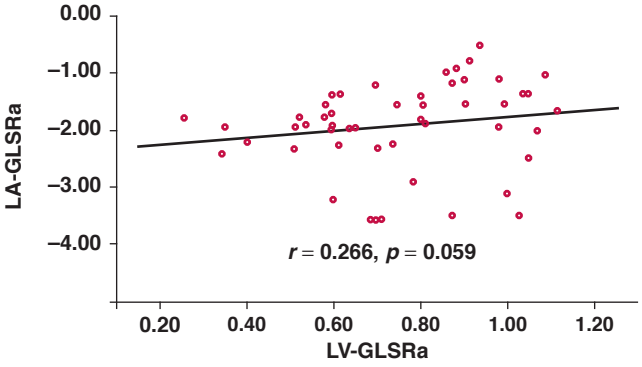

Fig. 8. Correlation between peak early diastolic strain rate of the left ventricle (LV-GLSRa) and peak early diastolic strain rate of the left atrium (LA-GLSRa) in patients with NSTEMI.

error.[19,20] Therefore, new methodologies that can evaluate LA function by analysis of LA myocardial deformation may be of potential clinical interest.

Two strain imaging methods are based on different principles and can potentially give different results. Tissue Doppler imaging (TDI)-derived strain is limited to the measurement of movement parallel to the ultrasound beam. Non-Doppler 2D strain imaging derived from speckle tracking is a newer echocardiographic technique for obtaining SR measurements. The advantage of this method is that it tracks in two dimensions, along the direction of the wall, not along the ultrasound beam, and thus is angle independent, which is a great advantage of non-Doppler 2D strain imaging in comparison to TDI-derived strain data.[2]

Previous studies show that 2D STE with its latest applications such as strain rate imaging may represent promising techniques to better evaluate LA function.[21] With the use of strain rate imaging, Inaba *et al.* found that SRs corresponded to reservoir function and SRe corresponded to conduit function, while SRa corresponded to booster pump function.[22]

In patients with AMI, left ventricular stroke volume is relatively maintained despite the impairment of left ventricular function caused by myocardial ischaemia and necrosis. With increased stiffness or reduced compliance of the LV, LA pressure rises to maintain adequate LV filling, and the increased atrial wall tension leads to chamber dilatation and stretch of the atrial myocardium.[23] Therefore, the left atrium works harder and transports more blood to the left ventricle during left ventricular diastole. This function of the left atrium can be attributed to the Frank-Starling mechanism. LA pump function augmentation is therefore due to the increased left atrial volume before active atrial emptying, but not to the increased contractility of the left atrium.[24]

In our study protocol, patients with NSTEMI showed increased LA volumes (LAV_{max}, LAV_{min} and LA_p). Moreover, indices of LA reservoir function (LA total EF) and LA conduit function (LAPEF) were significantly impaired and compared with healthy controls, but LA booster function (LAAEF) seemed to be unchanged in both normal subjects and patients (Table 2).

In accordance with the conventional echocardiographic parameters mentioned above, we found LA reservoir function assessed by SR imaging (LA-GLSRs) and LA conduit function assessed by SR imaging (LA-GLSRe) were significantly reduced in patients with NSTEMI (Table 4), but LA booster function assessed by SR imaging (LA-GLSRa) showed no significant difference. This may be explained by when the LA is well stretched longitudinally, and consequently a high LA positive peak is present, the LV then relaxes rapidly, generating a high E wave, as blood rushes into the LV, generating a high passive LA emptying fraction. Therefore, LA-GLSRs and/or LA-GLSRe have significant correlations with LV diastolic function, which are impaired in patients with NSTEMI.

In our study protocol, a good correlation was found between LA global strain rate and LA functional parameters (Table 5). The present study extends previous results and describes changes in LA function after AMI, combining LA volumes, LA emptying fraction, and LA strain in patients with NSTEMI. The results show that speckle tracking-derived strain rate is a promising technique to assess LA function as well as LA volumes and LA emptying fraction.

Global strain is a relatively new parameter for assessment of LV function[25] and tends to predict the infarct mass better than established indices of global function such as LVEF and WMSI. LVEF can be regarded as the sum of all LV systolic deformation.

In Wakami *et al*.'s study, peak LA strain rate during LV systole, which corresponds to our measured LA-GLSRs, correlated inversely with LV end-diastolic pressure and LV end-systolic volume and positively with LVEF.[26] In a recent study by Vartdal *et al*., global strain measured by TDI immediately after PCI was found to be superior to LVEF for predicting final infarct mass in patients with acute MI.[27] Comparing with tagged magnetic resonance imaging (the current 'gold standard' for deformation analysis), STE measurements correlated well with data obtained by magnetic resonance imaging, both in normal myocardial segments and infarcted areas ($r = 0.87$, $p < 0.001$).[28]

The findings of our present study are in accordance with previous studies. There was significant correlation between LVEF and global LA-GLSRs ($r = –0.334$, $p < 0.05$) or LA-GLSRe ($r = –0.477$, $p < 0.001$). In particular, LA-GLSRe was strongly correlated with LV-GLSRe ($r = –0.644$, $p = 0.001$), while LA-GLSRs and LA-GLSRa were not significantly correlated with LV strain rate parameters (LV-GLSRs and LV-GLSRa). These findings support the idea that LA-GLSRe can serve as an important new marker of LA and LV function in the acute MI.

Therefore, speckle tracking echocardiography was found to be a feasible and reproducible method to assess LA longitudinal strain in healthy subjects and patients with NSTEMI. The

reproducibility of measurements was good, with lower variability of intra- and inter-observer. In particular, we found LA-GLSRe was significantly correlated with both LA 2D Doppler echocardiographic parameters and LV contractile function, and could be an optimal parameter of 2D STE in assessing the degree of impairment of heart function in patients with NSTEMI. These data suggest that speckle tracking echocardiography may be considered a promising tool to explore LA myocardial deformation dynamics.

Study limitations

A number of obvious limitations of our study should be noted. First, the 2D STE analysis software that was originally designed for the left ventricle was applied to the left atrium in our study. Second, echocardiography in this study was not performed in the emergency room but on arrival at the coronary care unit or one to three days later. Third, the relatively small number of patients eligible for analysis in the present study may render it difficult to generalise the results and apply them to other patient populations. Further larger, prospective studies are required to determine the cost effectiveness of this new technique to evaluate LA function in NSTEMI patients. Lastly, this was a cross-sectional study, and therefore no clinical outcomes were examined.

Conclusions

Our study demonstrated that two-dimensional speckle tracking echocardiography represented a non-invasive, relatively simple and reproducible technique to assess left atrial myocardial function in patients with NSTEMI. Considering the limitations of classical indices of LA function, speckle tracking is easy to operate and has the advantage of being angle independent and less affected by reverberations. The reservoir and conduit function of the left atrium were impaired in these patients, compared with age-matched healthy controls. Importantly, LA-GLSRe was significantly correlated with both LA 2D Doppler echocardiographic parameters and LV contractile function and could be suggested as a better indicator to evaluate LA function as a preferred parameter of STE.

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A comparison between size of the occluder device and two-dimensional transoesophageal echocardiographic sizing of the ostium secundum atrial septal defect

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Abstract

Objectives: **Transcatheter closure of a secundum atrial septal defect (ASD II) has become an effective alternative for surgical treatment. In this study we evaluated the correlation between the two-dimensional transoesophageal echocardiographic (2D TEE) sizing of ASDs and the actual diameter of occluders in patients undergoing device closure.**

Methods: **The records of 54 patients who underwent transcatheter ASD closure were reviewed. ASD characteristics and maximum defect diameter were evaluated using pre-procedure 2D TEE images. Appropriate device size was determined by the balloon sizing method, which measures the balloon occlusive diameter (BOD) via TEE and fluoroscopy. ASD closure was performed under continuous TEE monitoring using the Amplatzer occluder in all patients.**

Results: **The mean of the TEE-derived maximum defect diameter was significantly lower than the mean of the BOD (17.8 ± 4.5 vs 22.1 ± 5.1 mm; $p < 0.001$) and the mean size of the implanted occluder device (17.8 ± 4.5 vs 23.3 ± 5.1 mm; $p < 0.001$). However, a good correlation was found between the TEE-derived defect size and the BOD (BOD = 0.898 × TEE defect size + 6.212, $R = 0.824$; $p < 0.001$) and between the TEE measurement and the final size of the implanted Amplatzer (device size = 0.928 × TEE defect size + 6.853, $R = 0.822$; $p < 0.001$).**

Conclusions: **2D TEE may provide a good equation to predict the BOD or the size of the occluder device; however, further studies are needed to investigate whether it is feasible to perform transcatheter ASD occlusion without balloon sizing.**

Keywords: atrial septal defect (ASD), occluder device, 2D TEE, balloon sizing

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Atrial septal defect (ASD) is one of the most common lesions in congenital heart disease.[1] The most frequent ASD is of the ostium secundum type (ASD II), which constitutes approximately 7% of all cases of congenital heart disease,[2] and is suited for transcatheter device closure.[3,4] Percutaneous closure of the ASD II has been accomplished safely and effectively using several different devices.[5-7]

Accurate measurement of the size of the defect is of paramount importance for the selection of an appropriate device and its subsequent successful deployment. Implanting too large a device may lead to a mushrooming deformity or cardiac perforation or it may increase the risk of device erosion over time,[8-10] while using too small a device has been accompanied by device instability, distal embolisation of the device, and residual shunting.[11,12] Balloon sizing of the defect has been considered the gold standard for measuring ASD size,[13-18] while angiography, transthoracic echocardiography (TTE), two- and three-dimensional transoesophageal echocardiography (TEE), intracardiac echocardiography, and intravascular ultrasound have been tried as guiding methods during the closure procedure.[10,14-16,18-20]

Stretched balloon diameter (SBD) and balloon occlusive diameter (BOD) are two measurements that have long been used by interventionalists in the selection of an appropriate device size for implantation.[17-19] However the balloon sizing method has its disadvantages. Inflation of the balloon may enlarge the defect, cause arrhythmias, or lead to hypotension due to decreased diastolic filling.[21,22] Some investigators therefore consider this cumbersome procedure unnecessary[7,23] and prefer less-invasive measuring methods in the selection of the size of the ASD closure device.[10,14,19,24]

TEE is crucial for the assessment of ASD morphology.[19,23,25] Many studies have indicated the highly reliable role of TEE in the prediction of BOD, SBD and device size.[10,15,17,19]

We previously investigated the association between the BOD and pre-procedure TEE-estimated defect size in a study with a smaller sample size.[26] The main aim of the current study was to compare the ASD II diameter obtained via TEE and the deployed device size, and subsequently devise a formula for estimating the appropriate device diameter using TEE measurement.

Methods

We retrospectively reviewed the records of patients with ASD II considered for device placement at our institution from July

2005 to February 2010. Of 60 patients, 54 (12 male and 42 female) underwent successful transcatheter closure (device in proper position and no or trivial shunt across the septum) and were included in our study. The procedure failed in four cases due to insufficient support of the device by the interatrial septum, and two other patients underwent open-heart surgery because the device had embolised to the left atrium.

Before the procedure, all the patients underwent a comprehensive transoesophageal echocardiographic study to investigate the morphology of the defect. Based on availability, 36 patients underwent ASD closure using the Amplatzer septal occluder, whereas 18 patients had its Chinese copycat, the Heart® ASD occluder device. Pre-discharge echocardiography was done 24–48 hours after the procedure.

Echocardiographic assessment was conducted in all patients, using a combination of two-dimensional (2D) transthoracic (Vingmed GE, Horten, Norway, 3.5-MHz transducer) and transoesophageal echocardiography (Vivid-7, Vingmed GE, Horten, Norway, 7-MHz transducer). All patients were reassessed between 24 hours and six weeks after PTMC via transthoracic echocardiography. All echocardiographic measurements were assessed based on the American Society of Echocardiography (ASE) guidelines and standards.

TEE was performed within the six-month period before the transcatheter occlusion procedure, to exclude other associated cardiovascular deformities and to investigate the suitability of the ASD size and its surrounding rims for transcatheter closure. Under local anaesthesia, 2D TEE was performed and the diameter of the defect was measured in various planes to determine the maximal defect size. The most useful views for defect sizing included the mid-oesophageal four-chamber view at 0°, the short-axis view at 45–60°, and the bicaval long-axis view at 90–110°.

The maximal diameter of the defect was acquired during the cardiac cycle and recorded. The rims of the defect were measured from the margins of the defect to the inferior vena cava, superior vena cava, right upper pulmonary vein, tricuspid and mitral valves, aorta, and coronary sinus, wherever possible. Exclusion criteria for device closure comprised (1) ASD rims ≤ 5 mm, except for the anterior superior rim, and (2) multiple ASDs as assessed by TEE.

Balloon sizing and deployment of the septal occluder

Vascular access was obtained from the femoral vein. The tubular sizing balloon (AGA Medical Corporation, Golden Valley, MN, USA) was introduced over a wire that had been placed through the ASD into a left pulmonary vein. Under transoesophageal echocardiographic guidance, the balloon was inflated in the left atrium with increasing quantities of diluted contrast medium and was then pulled back against the ASD. It was thereafter deflated to reach a size sufficient to enable it to be pulled into the right atrium through the defect.

The BOD was defined as the balloon size that completely occluded the ASD and prevented any shunt across the defect without deformity of the balloon. The balloon diameter was measured directly on the screen connected to fluoroscopy and by TEE. Device size was selected with a waist diameter similar to or up to 3 mm larger than the BOD measurement, according to the flexibility of the surrounding rims. Subsequently, the device was inserted and deployed under TEE guidance.

The technique of device closure was similar to those described in the literature.[6,27] Based on availability, the Amplatzer septal occluder (AGA Medical Corporation, Golden Valley, MN, USA) or its Chinese copycat, the Heart® ASD intracardiac patch occluder (Lifetech Scientific INC, Shenzhen, China), were implanted in patients. After releasing the device from the cable, a final TEE examination was undertaken to ascertain the position of the device and any residual shunting.

Successful ASD closure was defined as a device in the proper position with no or trivial leak, as determined by TEE in the catheterisation laboratory. Following the procedure, the patients were sent to a recovery room with ECG monitoring for 12 hours and were discharged two days after the procedure. All patients underwent TTE before discharge.

Statistical analysis

The numerical variables are presented as mean ± SD (standard deviation), while the categorical variables are summarised by raw numbers and percentages. The paired *t*-test was used to compare ASD size by TEE and by the diameter of the deployed device or via balloon sizing. The linear regression analysis was performed to demonstrate the relationship between TEE size and BOD and also between TEE measurement and final size of the implanted device.

The measured and calculated (predicted) ASD device diameters were further examined by plotting scattergrams and developing regression lines. The statistical software SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL) was used for the statistical analysis and a p-value ≤ 0.05 was considered statistically significant.

Results

Fifty-four patients (12 male and 42 female) aged nine to 71 years fulfilled the inclusion criteria. All the patients underwent successful ASD closure under 2D TEE monitoring. Maximum defect size ranged between 10 and 30 mm. The devices were deployed appropriately (range of size: 14–39 mm) with no residual shunt across the septum except in one patient who had a trivial shunt just after the occlusion procedure.

Under pre-discharge TTE evaluation, there was no report of any shunt; and mild pericardial effusion occurred in three patients, while moderate pericardial effusion was detected in one patient. In one subject, there was mild compressive effect on the aortic root and in another there was compressive effect on the aortic root, at the base of the anterior mitral leaflet and base of the septal tricuspid leaflet. All these patients were followed up meticulously and these events resolved spontaneously.

Demographic data, and echocardiographic and ASD characteristics of all patients are summarised in Table 1. The mean of TEE-derived maximum size of the defect was lower than the mean of the BOD (17.8 ± 4.5 vs 22.1 ± 5.1 mm; $p < 0.001$) and also lower than the mean size of the implanted device (17.8 ± 4.5 vs 23.3 ± 5.1 mm; $p < 0.001$) (Table 1). There were good correlations between maximum defect size measured on TEE and via balloon sizing (BOD = 0.898 × TEE defect size + 6.212, $R = 0.824$; $p < 0.001$) and between TEE diameter and the final size of occluded device (device size = 0.928 × TEE defect

TABLE 1. DEMOGRAPHIC, ECHOCARDIOGRAPHIC AND ASD CHARACTERISTICS OF PATIENTS

	Cases (n = *54*)
Age (years)	34.5 ± 14.0
Male gender	12 (22.2)
Ejection fraction (%)	55.6 ± 4.4
Left ventricular systolic dimension (mm)	25.6 ± 3.8
Left ventricular diastolic dimension (mm)	38.4 ± 5.3
Pulmonary artery pressure (mmHg)	43.3 ± 12.5
Pulmonary-to-systemic blood flow	2.1 ± 0.6
Right ventricular dimension (mm)	38.3 ± 5.6
Tricuspid annular plane systolic excursion (TAPSE) (mm)	25.9 ± 8.8
Pulmonary artery diameter (mm)	33.1 ± 9.0
TEE-derived max defect size (mm)	17.8 ± 4.5*+
Balloon occlusive diameter (BOD) (mm)	22.1 ± 5.1+
Device size (mm)	23.3 ± 5.1

Data are presented as mean ± SD or *n* (%). TEE: transoesophageal echocardiography; *$p < 0.001$ compared to the BOD; +$p < 0.001$ compared to the device size.

size + 6.853, $R = 0.822$; $p < 0.001$); Fig. 1 depicts the respective information.

Discussion

Our results show that the mean TEE-derived size of the ASD was significantly lower than both the mean diameter of ASD obtained via balloon sizing and the mean size of the implanted device. There was good correlation between TEE sizing of the ASD and the diameter of the deployed device, which makes it feasible to propose a formula that could be used for the prediction of device size in ASD occlusion procedures. However it is not sufficient to predict the exact size of device prior to ASD closure via echocardiographic evaluation.

In line with our results, some reports have previously indicated that TEE underestimates ASD size in comparison with the SBD obtained during catheterisation.[18,28] TEE allows only a limited view of the ASD morphology. The maximum ASD size might therefore be underestimated if the probe is not in the same plane as the largest diameter of the ASD.[18] It could also be attributed to the intact anatomy of the ASD during echocardiographic evaluation, in contrast with the disturbed anatomy during device implantation, which pushes the atrial walls away.

Accordingly, previous studies have revealed a good linear correlation between TEE-derived ASD size and balloon-sizing measurements,[10,15,29] and have also evaluated correlations between TEE measurements and the diameter of the Amplatzer occluder device. They proposed the following equations to calculate proper device size: device size = 2.76 + 1.16 × TEE defect size, $R^2 = 0.91$;[10] device size = 4.08 + 1.05 × TEE defect size, $R = 0.91$.[19]

The results of the present study confirm these findings, with some minor differences in the equations. These differences might be attributed to different sample sizes, technical methods, and institution standards. Likewise, several other investigators have confirmed the accuracy of SBD prediction[17] or occluder device size,[10,19] based on echo measurements.

Some limitations inherent to our study must be taken into account. We only reviewed the records of 54 patients, whose procedures were not performed by a single operator. Consequently, potential differences in the physicians' experience levels and in the patient population might have been responsible for the minor differences between our formula and the formulae proposed by other investigators.

We excluded multiple ASDs on account of the fact that accurate assessment of the defect diameter in these situations was difficult to obtain. The suitability of TEE for the sizing of multiple defects therefore remains to be elucidated. In addition, the long-term results of transcatheter ASD closure without balloon sizing have not been investigated extensively and await further studies.

Conclusion

Based on this study, a good formula was developed that correlates TEE measurements of ASD and the size of the implanted device. However further studies are needed to elucidate whether or not this formula alone can be used to replace balloon sizing of ASDs.

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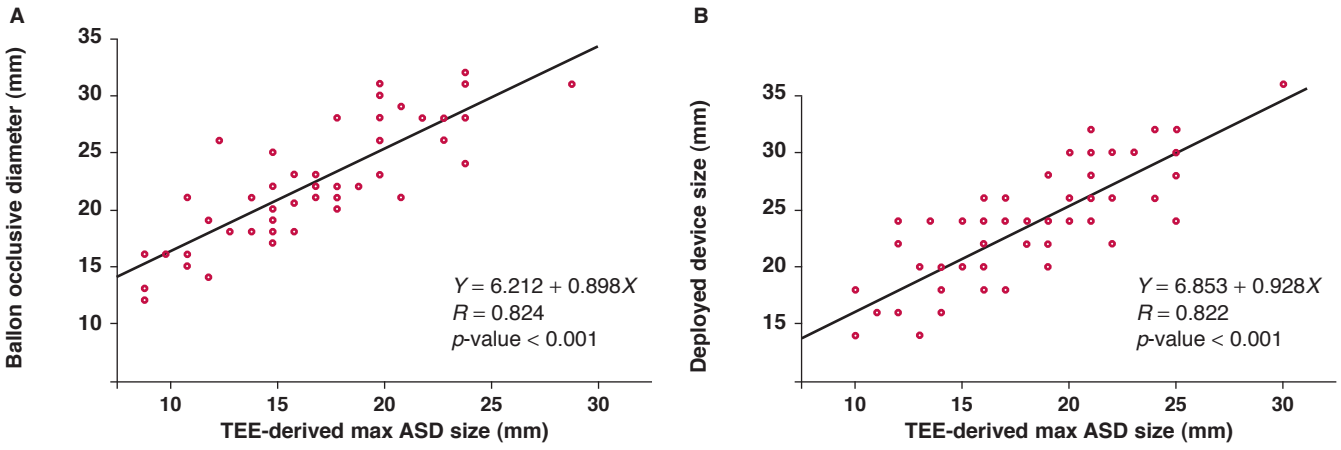

Fig. 1. The relationship between final device size and maximal ASD diameter measured via (A) TEE, (B) balloon sizing.

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The optimal time of B-type natriuretic peptide sampling associated with post-myocardial infarction remodelling after primary percutaneous coronary intervention

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Abstract

Aims: **To find the optimal time to evaluate plasma B-type natriuretic peptide (BNP), which is related to post-myocardial infarction remodelling (PMIR), we measured serial plasma BNP levels according to time protocols after primary percutaneous coronary intervention (PCI).**

Background: **It has been established that plasma BNP levels can predict the development of PMIR in patients with ST-elevation myocardial infarction (STEMI). However, the time of plasma BNP sampling associated with PMIR is still controversial.**

Methods: **We analysed 42 patients who were diagnosed as PMIR on six-month follow-up echocardiography among 131 patients with STEMI. We then compared clinical variables including plasma BNP between the remodelling group and the non-remodelling group. The plasma BNP level was obtained on hospital admission (acute phase), at two to five days (early phase), three to four weeks (late phase) and at the six-month follow up (long term).**

Results: **Early-phase and long-term BNP levels were higher in the remodelling group. The serial plasma BNP levels, according to study protocols, showed a biphasic pattern of elevation. In multiple logistic regression analyses, early-phase BNP [odds ratio (OR): 1.013, $p < 0.01$] and acute-phase BNP levels (OR: 1.007, $p = 0.02$) were independent predictors of PMIR. However, early-phase BNP level was statistically a more powerful predictor of PMIR during follow up.**

Conclusion: **Consecutive BNP levels after primary PCI showed a biphasic peak elevation during follow up. Early-phase plasma BNP level was an independent predictor of PMIR in patients with STEMI.**

Keywords: B-type natriuretic peptide, remodelling, myocardial infarction

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Post-myocardial infarction remodelling (PMIR) in patients with ST-elevation myocardial infarction (STEMI) is detrimental to normal left ventricular (LV) systolic function and is associated with heart failure and death due to cardiovascular events.[1] Although an early reperfusion strategy such as primary percutaneous coronary intervention (PCI) has become widespread in recent years, a significant percentage of STEMI patients still suffer from PMIR.

Anterior wall infarction, peak levels of creatine kinase myocardial band (CK-MB) and troponin I, LV systolic dysfunction, and wall motion score index (WMSI) have been associated with the development of PMIR.[2] Also, increased expression of B-type natriuretic peptide (BNP) has been suggested to be an indicator of PMIR, so plasma BNP levels can be used as diagnostic and monitoring tools for PMIR in patients with STEMI.[3,4]

Plasma BNP levels in patients with STEMI have shown a positive correlation with the degree of LV systolic and diastolic dysfunction.[5] Although the prognostic significance of BNP levels has been elucidated, a suitable point in time for BNP sampling related to PMIR has not been established. Several studies have reported that plasma BNP levels measured at hospital admission or in the acute phase were meaningful predictors of PMIR,[5,6] whereas others have stated that later sampling during follow up was associated with PMIR.[7,8]

We evaluated serial changes in plasma BNP levels after successful revascularisation using primary PCI. We identified a suitable point in time for BNP sampling as an independent predictor of PMIR in patients with STEMI.

Methods

The research protocol was approved by the Committee on Ethics and Research of Wonju Christian Hospital (Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea). Written informed consent was obtained from each patient.

One hundred and thirty-one STEMI patients were the study subjects. All patients were admitted to Wonju Christian Hospital. They had received reperfusion therapy using primary PCI within 12 hours of symptom onset and had blood sampling with a planned schedule for BNP. We then compared clinical variables including plasma BNP levels and echocardiographic data between the remodelling (RG) and non-remodelling groups (NRG). The study period was from April 2006 to March 2009.

Inclusion criteria were ischaemic chest pain lasting ≥ 30 min; electrocardiographic ST-segment elevation > 0.1 mV in two or more limb leads, or > 2 mV in two or more precordial leads or new-onset left bundle branch block; and elevation in the level of CK-MB or troponin I to ≥ twice the normal range.

Exclusion criteria were previous myocardial infarction (MI); severe valvular heart disease; cardiomyopathy; impaired renal function (creatinine > 1.5 mg/dl); inadequate quality of echocardiographic images; cardiogenic shock (initial systolic blood pressure < 90 mmHg); advanced heart failure (Killip class ≥ III); or life-limiting non-cardiac disease.

Success of revascularisation using primary PCI was defined as residual stenosis < 50% and if coronary flow in the culprit vessel after primary PCI resulted in thrombolysis in myocardial infarction (TIMI) grade ≥ 2. The primary PCI procedure and type of stent used were at the discretion of the interventional cardiologist.

Coronary angiographic analysis during primary PCI was performed by interventional cardiologists in the Ilsan Paik Hospital cardiovascular centre, who were blinded to clinical and plasma BNP findings. All patients were prescribed aspirin (300 mg p.o.), clopidogrel (600 mg p.o.), and heparin (70 IU/kg p.o.) before the procedure. Each patient was maintained on aspirin (100 mg) and clopidogrel (75 mg) for ≥ 12 months after revascularisation. Also, most patients received β-blockers, calcium-channel blockers, angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs), and statins at the discretion of the attending physician.

Blood samples were taken for BNP measurement on hospital admission (acute phase), at two to five days (early phase), three to four weeks (late phase), and at six months (long term) after symptom onset. All plasma samples were obtained in plastic tubes containing potassium ethylene diamine tetra-acetic acid (EDTA; Becton Dickinson, Franklin Lakes, NJ, USA) with amounts that ranged from 3–5 ml. All samples were centrifuged, and plasma was tested singly for BNP using the Biosite Triage Assay, a point-of-care device that uses a fluorescence immunoassay technique (Biosite, San Diego, CA, USA).

The total coefficient of variation at different levels of plasma BNP was reported to be < 7% using control samples provided by the manufacturer. The sensitivity for BNP in these measurements ranges from 5–5 000 pg/ml. Levels of CK-MB and troponin I were evaluated after symptom onset. The peak release of CK-MB and troponin I was determined every four hours after hospital admission for three days.

Two-dimensional echocardiography was undertaken at baseline and at the six-month follow up. Echocardiographic examinations and data were obtained using a commercially available imaging system (Vivid 7; GE Medical Systems, Milwaukee, WI, USA). Echocardiograhic data were sent to the echocardiography laboratory in Ilsan Paik Hospital cardiovascular centre and analysed by echocardiography physicians blinded to the laboratory data.

Apical four- and two-chamber views as well as apical long-axis views were obtained from all patients. To assess regional wall motion abnormalities, the wall of the LV was divided into 16 segments, as recommended by the American Society of Echocardiography.[9] For each segment, the WMSI was derived. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LV ejection fraction (LVEF) were calculated using a modified version of Simpson's method.

Assessment of diastolic function was carried out by measuring the mitral inflow pattern with pulsed-wave Doppler [E/A ratio, and deceleration time (DT) of the E wave], pulmonary venous inflow, and tissue Doppler velocities of the mitral annulus. The ratio of early diastolic mitral annulus velocity (E/E′) was used as an indicator for LV filling pressures.[10]

PMIR was defined as > 20% increment in LVEDV estimated at the six-month follow-up echocardiography compared with baseline results using a modified version of Simpson's method.[2] Intra- and inter-observer variability of LVEDV and LVESV was < 5% in this study.

Statistical analyses

Data were analysed using the SPSS statistical package, version 15.0 (SPSS Incorporated, Chicago, IL, USA). Data are mean ± SD for continuous variables and frequency with percentages for categorical variables. Because mean BNP levels were uneven, natural log transformation was used in the regression analyses to satisfy modelling assumptions.

Continuous variables were compared using the paired Student's *t*-test. Categorical variables were compared using chi-square analyses. Differences in proportions were compared using Pearson's chi-square test. Repeated-measures analysis of variance (ANOVA) was used to analyse inter- and intra-group differences between the RG and NRG with regard to plasma BNP levels; $p < 0.05$ was considered significant. Univariate and multiple logistic regression analyses were carried out to estimate independent predictors of PMIR. Variable selection in multivariable modelling was based on statistical significance from univariate analysis.

The optimal time of BNP sampling for the prediction of PMIR was determined by a multivariate model. The BNP cut-off value for prediction of PMIR was assessed by receiver operator characteristic (ROC) curve analyses. The predictive value of plasma BNP level for PMIR was evaluated using estimation of the area under the curve (AUC) separately for each parameter.

Results

The clinical characteristics of the study population are shown in Table 1. All patients treated with primary PCI received at least one stent implantation. PMIR was detected in 42 patients. The mean age was older in the RG (RG vs NRG; 63.1 ± 11.9 vs 58.1 ± 11.1 years, $p = 0.02$). The mean time from symptom onset to reperfusion was later in the RG, but was not statistically significant (RG vs NRG; 5.4 ± 2.3 vs 4.8 ± 2.2 h, $p = 0.07$).

There were significant differences in the percentage of New York Heart Association class I between the two groups (RG vs NRG 57.1 vs 78.7%, $p = 0.03$). Moreover, mean peak levels of CK-MB (RG vs NRG; 246.8 ± 88.1 vs 170.9 ± 109.9 ng/ml, $p < 0.01$) and troponin I (RG vs NRG; 48.3 ± 28.3 vs 33.7 ± 25.1 ng/ml, $p < 0.01$) were significantly higher in the RG. At hospital

discharge, all patients received aspirin and clopidogrel, and there was no statistical difference in percentage use of β-blockers, ACEIs, ARBs, diuretics and statins between the two groups.

The baseline angiographic and procedural characteristics of the study population are listed in Table 2. With regard to the extent of coronary artery disease (CAD), the proportion of multi-vessel disease was similar between the two groups [RG vs NRG; 41.6% (n = 17) vs 42.9% (n = 37), p = 0.79]. In the RG, the most frequently involved coronary artery was the left anterior descending artery [RG vs NRG; 61.9% (n = 26) vs 42.7% (n = 38), p = 0.04].

Almost 90% of patients who underwent primary PCI received drug-eluting stent (DES) implantation. No difference was observed in terms of the proportion of DES or bare-metal stent (BMS) implantation between the two groups. Compared with a zotarolimus-eluting stent (ZES), we mainly used a sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES).

In addition, the final thrombolysis in myocardial infarction (TIMI) grade 3 flow after primary PCI [RG vs NRG; 85.7% (n = 36) vs 94.4% (n = 84), p = 0.09] and the number of stents per patient (RG vs NRG; 1.25 ± 0.53 vs 1.27 ± 0.36, p = 0.33) showed no significant differences between the two groups. We seldom used 2b/3a glycoprotein inhibitors during primary PCI [RG vs NRG; 9.5% (n = 4) vs 7.9% (n = 7), p = 0.78].

Baseline and follow-up haemodynamic parameters as well as diastolic dysfunction of the study population are listed in Table 3. Mean baseline LVESV and E/E′ were significantly higher in the RG than in the NRG. Also, mean baseline LVEF was significantly reduced in the RG. Follow-up echocardiography was performed at a mean of 6.5 ± 1.1 months after primary PCI.

At the six-month follow up, LVESV and LVEDV in the RG were increasing compared with baseline values. Mean six-month follow-up LVEF did not show notable changes compared with baseline. Although baseline diastolic dysfunction was not significantly different between the two groups, six-month follow-up diastolic dysfunction in the NRG showed a notable improvement. Mean six-month follow-up E/E′ in the RG was decreased in both groups, but mean E/E′ was significantly higher in the RG (RG vs NRG; 11.2 ± 6.2 vs 7.9 ± 3.8, p < 0.01).

Mean time of plasma BNP measurements in the early phase was 2.8 ± 0.5 days, in the late phase 3.7 ± 0.6 weeks, and long-term 6.3 ± 0.6 months after symptom onset. In the RG, mean plasma log BNP levels were significantly elevated in the acute (RG vs NRG; 1.77 ± 0.67 vs 1.29 ± 0.53, p < 0.01) and early phase (RG vs NRG; 2.31 ± 0.54 vs 1.56 ± 0.55, p < 0.01), and long term (RG vs NRG; 2.07 ± 0.55 vs 1.37 ± 0.46, p < 0.01) (Fig. 1).

Mean plasma BNP levels were significantly different between the two groups (p < 0.01, repeated measures ANOVA) and during each time phase (p < 0.01, repeated measures ANOVA). Compared with the NRG, the RG mean plasma BNP levels were prominently elevated in the early phase and long term. This biphasic peak elevation of plasma BNP level was a characteristic feature of the RG. As we examined plasma BNP measurements throughout each study period, plasma BNP levels in the RG were consistently higher than in the NRG.

Univariate regression analyses were conducted to determine a surrogate marker for PMIR independent of other predictors. The age, time from symptom to reperfusion, peak levels of troponin I and CK-MB, LVEF and E/E′ were significantly associated with PMIR at the six-month follow up.

Hierarchical multiple regression analyses for optimal time of PMIR were constructed (Table 4). In the multivariate model, after

TABLE 1. BASELINE CLINICAL CHARACTERISTICS BETWEEN NON-REMODELLING AND REMODELLING GROUPS

Variable	*Non-remodelling group* (n = *89*)	*Remodelling group* (n = *42*)	p
Age (years)	58.1 ± 11.1	63.1 ± 11.9	0.02
Males, *n* (%)	68 (76.4)	26 (61.9)	0.14
Diabetes mellitus, *n* (%)	26 (29.2)	10 (23.8)	0.68
Hypertension,* *n* (%)	46 (51.7)	18 (42.9)	0.35
Current smoker, *n* (%)	49 (55.1)	23 (54.8)	0.47
Hypercholesterolaemia,† *n* (%)	49 (55.1)	22 (52.4)	0.45
Time from symptom onset to to reperfusion (h)	4.8 ± 2.1	5.4 ± 2.3	0.07
Killip class I, *n* (%)	41 (44.9)	17 (40.5)	0.26
NYHA class I, *n* (%)	70 (78.7)	24 (57.1)	0.03
Peak CK-MB (ng/ml)	170.9 ± 109.9	246.8 ± 88.1	< 0.01
Peak troponin I (ng/ml)	33.7 ± 25.1	48.3 ± 28.3	< 0.01
Discharge medications			
Aspirin, *n* (%)	89 (100)	42 (100)	
Clopidogrel, *n* (%)	89 (100)	42 (100)	
β-blockers, *n* (%)	81 (91.1)	36 (85.7)	0.22
ACEIs or ARBs, *n* (%)	85 (95.5)	38 (90.5)	0.49
Diuretics, *n* (%)	44 (49.4)	22 (52.4)	0.41
Statins, *n* (%)	86 (96.6)	40(97.6)	0.86

Data are mean ± SD or numbers (percentage).
*Systolic pressure > 140 mmHg and/or diastolic pressure > 90 mmHg or receiving antihypertensive drugs.
†Total cholesterol > 220 mg/dl and/or low-density lipoprotein cholesterol > 130 mg/dl or receiving statin therapy.
NYHA, New York Heart Association; CK-MB, creatinine kinase myocardial band; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

TABLE 2. BASELINE PROCEDURAL CHARACTERISTICS BETWEEN NON-REMODELLING AND REMODELLING GROUPS

Variable	*Non-remodelling group* (n = *89*)	*Remodelling group* (n = *42*)	p
Multi-vessel disease, *n* (%)	37 (41.6)	18 (42.9)	0.79
IRA			
LAD, *n* (%)	38 (42.7)	26 (61.9)	0.04
LCX, *n* (%)	7 (7.9)	5 (11.9)	0.40
RCA, *n* (%)	44 (49.4)	11 (26.2)	0.01
Stent type (%)			
DES, *n* (%)	81 (91.1)	38 (90.5)	0.72
BMS, *n* (%)	8 (8.9)	4 (9.5)	0.69
DES type (%)			
SES, *n* (%)	29 (35.8)	16 (42.1)	0.43
PES, *n* (%)	39 (48.1)	18 (47.4)	0.47
ZES, *n* (%)	13 (16.1)	4 (10.5)	0.25
TIMI grade 3 after PCI, *n* (%)	84 (94.4)	36 (85.7)	0.09
Number of stents	1.25 ± 0.53	1.27 ± 0.36	0.33

Data are mean ± SD or numbers (percentage).
IRA, infarct-related artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; BMS, bare-metal stent; DES, drug-eluting stent; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; ZES, zotarolimus-eluting stent; TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention.

TABLE 3. BASELINE AND FOLLOW-UP ECHOCARDIOGRAPHIC CHARACTERISTICS BETWEEN NON-REMODELLING AND REMODELLING GROUPS

Variable	*Non-remodelling group* (n = *89*)	*Remodelling group* (n = *42*)	p
Haemodynamics			
Baseline			
LVESV (ml)	31.6 ± 16.8	37.2 ± 19.2	0.03
LVEDV (ml)	71.1 ± 20.2	74.4 ± 16.1	0.36
LVEF (%)	57.0 ± 9.5	50.3 ± 9.3	0.00
DT (ms)	211.7 ± 42.7	203.9 ± 46.1	0.10
E/E′	11.0 ± 4.3	14.5 ± 2.8	< 0.01
Follow up			
LVESV (ml)	28.9 ± 14.2	49.3 ± 17.3	< 0.01
LVEDV (ml)	69.9 ± 19.3	94.7 ± 21.4	< 0.01
LVEF (%)	60.2 ± 10.6	48.9 ± 10.7	< 0.01
DT (ms)	236.7 ± 42.0	204.7 ± 49.3	< 0.01
E/E′	7.9 ± 3.8	11.2 ± 6.2	< 0.01
Diastolic dysfunction (%)			
Baseline			
Grade 1 (%)	56 (62.9)	21 (50.0)	0.16
Grade 2 (%)	22 (24.7)	17 (40.5)	0.07
Grade 3 (%)	0 (0)	2 (4.8)	0.04
Follow up			
Grade 1 (%)	76 (85.4)	26 (61.9)	< 0.01
Grade 2 (%)	3 (3.4)	9 (21.4)	< 0.01
Grade 3 (%)	0 (0)	5 (11.9)	< 0.01

Data are mean ± SD or numbers (percentage).
LV, left ventricular; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction; DT, deceleration time.

adjusting for age, gender, time from symptom to reperfusion, troponin I level, CK-MB level, LVEF, E/E′ and WMSI, acute- and early-phase BNP were identified as independent predictors of PMIR at the six-month follow up.

Among the time phases, early-phase BNP was a meaningful predictor of LV remodelling. ROC curves for early-phase plasma BNP levels for the prediction of PMIR are shown in Fig. 2. The AUC of early-phase BNP levels for predicting PMIR was 0.83 with a cut-off value of 172.9 pg/ml. Early-phase plasma BNP levels showed a sensitivity of 76.2% and a specificity of 74.2%.

TABLE 4. MULTIPLE LOGISTIC REGRESSION ANALYSIS TO EVALUATE THE TIME POINT OF PLASMA BNP SAMPLING THAT IS CLOSELY ASSOCIATED WITH LV REMODELLING. STEPWISE ADJUSTMENT OF DIFFERENT FACTORS INCLUDING AGE, GENDER, TIME FROM SYMPTOM ONSET TO REPERFUSION, CK-MB LEVEL, TROPONIN-I LEVEL, E/E′ AND WMSI

Variable	*Odds ratio*	*95% Confidence interval*	*p*
Model 1			
Age, gender adjusted			
Acute BNP	1.006	1.001–1.011	0.02
Early BNP	1.011	1.007–1.016	< 0.01
Late BNP	1.005	0.998–1.011	0.15
Long-term BNP	1.010	1.004–1.016	0.01
Model 2			
Time from symptom onset to reperfusion adjustment			
Acute BNP	1.005	0.999–1.010	0.08
Early BNP	1.011	1.006–1.016	< 0.01
Late BNP	1.004	0.997–1.010	0.24
Long-term BNP	1.009	1.002–1.015	0.01
Model 3			
Tn-I, CK-MB adjusted			
Acute BNP	1.008	1.002–1.014	0.01
Early BNP	1.012	1.006–1.018	< 0.01
Late BNP	1.004	0.997–1.012	0.22
Long-term BNP	1.007	1.001–1.014	0.03
Model 4			
LVEF-, E/E′-, WMSI-adjusted			
Acute BNP	1.007	1.001–1.014	0.02
Early BNP	1.013	1.006–1.019	< 0.01
Late BNP	1.004	0.996–1.012	0.36
Long-term BNP	1.005	0.998–1.012	0.13

*p-values are based on the multiple regression analysis. BNP, B-type natriuretic peptide; Tn-I, troponin I; CK-MB, creatinine kinase myocardial band; LVEF, left ventricular ejection fraction.

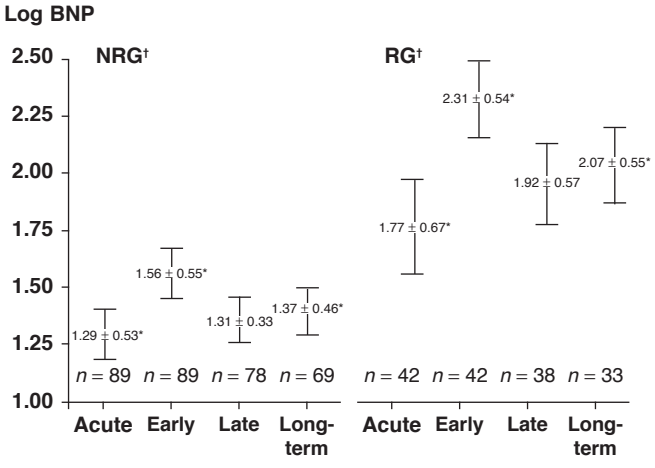

Fig. 1. Serial changes in plasma log BNP levels according to left ventricular remodelling. *$p < 0.01$ for the comparison of plasma log BNP levels between groups. †$p < 0.01$ for inter- and intra-group differences during the study period. BNP, B-type natriuretic peptide; NRG, non-remodelling group; RG, remodelling group. Data are mean ± SD.

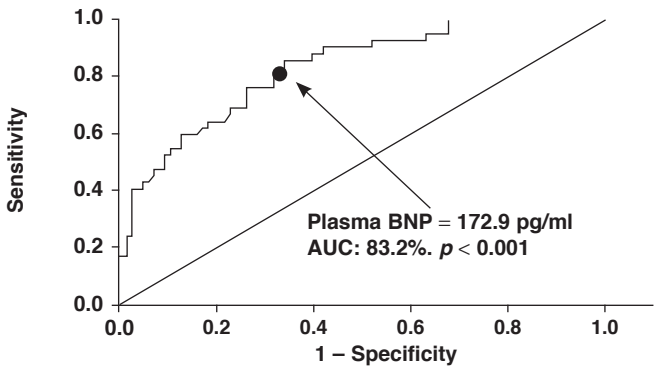

Fig. 2. From the ROC curve, the diagnostic accuracy of the early-phase plasma BNP level for predicting LV remodelling in patients with STEMI was 83.2% (sensitivity 76.2%; specificity 74.2%), and the optimum cut-off point was 172.9 pg/ml ($p < 0.01$). ROC, receiver operator characteristic; BNP, B-type natriuretic peptide; AUC, area under the curve.

Discussion

The main finding of the present study was that the appropriate plasma BNP sampling time that reflected the development of PMIR in patients with STEMI was the early phase, from two to five days after the onset of STEMI. Several studies focusing on the association between plasma BNP and PMIR have confirmed that elevated BNP is a marker for LV systolic dysfunction and a significant prognostic marker for morbidity and mortality in patients with STEMI.[11,12] However, some discrepancies exist in the optimal time point of plasma BNP sampling that is associated with the prediction of PMIR.

Some studies reported that plasma BNP levels at one to four days were strongly related to PMIR after STEMI.[13-15] Other studies suggested that plasma BNP levels on hospital admission were associated with PMIR at the six-month follow up in patients with STEMI.[5,16] One study demonstrated that BNP sampling three to four weeks after the onset of STEMI was significantly correlated with PMIR.[7]

The results of the present study conflict with several studies reporting that BNP sampling three to four weeks after the onset of STEMI was significantly correlated with PMIR. Although our results showed concordance between plasma BNP levels at hospital admission and PMIR, plasma BNP levels measured from two to five days represented a more powerful predictor of PMIR in patients with STEMI. These discrepancies may have been due to an inhomogeneous study population, varying time from symptom onset to reperfusion, reperfusion strategy, infarct-related arteries, underlying medical conditions, and timing of BNP measurement.

Plasma BNP level was increased in the acute and early phase and decreased during follow up in the present study. Plasma BNP may be synthesised in the ventricular myocardium and released into the bloodstream in response to multiple stimuli, including ischaemia, inflammation, ventricular volume overload, pressure overload, and reperfusion injury.[17,18] Myocardial ischaemia, the inflammatory response, ventricular volume overload or pressure overload before reperfusion may occur simultaneously in patients with STEMI. Importantly, myocardial ischaemia and inflammatory stimuli can be aggravated by reperfusion during primary PCI.[19]

Microcirculatory obstruction may occur via distal embolisation, and infarct expansion during PCI may affect the elevation of plasma BNP levels.[20] Post-PCI plasma BNP level was consistently higher than pre-PCI plasma BNP level in patients with STEMI, and those who showed elevated post-PCI plasma BNP levels were expected to undergo PMIR or cardiac death.[21]

Accumulation of intracellular calcium in infarcted myocardium before reperfusion does not stimulate or increase the synthesis and secretion of BNP in the plasma.[22] Even if plasma BNP level at hospital admission could be a sufficient surrogate marker for PMIR, it cannot reflect a broad spectrum of myocardial damage, including reperfusion injury.

Plasma BNP levels after reperfusion in STEMI appeared to be higher in our study than in several studies on patients with acute or chronic heart failure.[15,23] Hence, myocardial ischaemia may be a stronger factor than ventricular volume overload or pressure overload as a stimulus for BNP secretion. Therefore, ventricular volume overload or pressure overload before reperfusion may be non-specific in Killip class I–II or in haemodynamically stable patients with STEMI.

Plasma BNP level measured from two to five days after reperfusion correlated not only with ischaemic injury but also reperfusion injury. This may be important for using post-PCI plasma BNP level as an integrated biomarker of total myocardial damage. Also, we demonstrated that plasma BNP level could be a useful and significant predictor of PMIR that was not inferior or superior to other established predictors, including age, peak level of CK-MB and troponin I reflecting infarct size, as well as echocardiographic LVEF and diastolic filling parameters.

Studies in STEMI and non-STEMI patients have demonstrated that a biphasic pattern of plasma BNP levels reflects the major damage to the myocardium and subsequent LV systolic dysfunction.[4,24] Peak plasma BNP elevations in the present study were observed in the early phase and long term during the follow-up periods. Compared with the NRG, plasma BNP levels were more prominent in the early and long-term phases, so the pattern of plasma BNP elevation was similar to that observed in the previous study. Although BNP level three to four weeks after the onset of STEMI reflecting the second peak of plasma BNP has been reported,[7] plasma BNP level at six months after the onset of STEMI appeared to represent the second peak in the current study.

It has been reported that Doppler-derived E/E′,[25] and DT[26] are relevant measurements of elevated LV filling pressure and LV dilation in patients with STEMI. We also evaluated and analysed the diastolic parameters of echocardiography for the prediction of PMIR. Among the parameters, initial Doppler-derived E/E′ was significantly correlated with PMIR in a multiple regression model. Although studies have suggested that Doppler-derived DT is closely related to the risk of PMIR after STEMI, DT cannot reflect elevated mean LV diastolic pressure in patients with preserved systolic function.[25,26] In the present study, plasma BNP levels at two to five days and initial Doppler-derived E/E′ proved to be significant predictors of PMIR.

We focused on the background of post-PCI plasma BNP elevation after successful coronary reperfusion. Although primary PCI is the optimal therapy in patients with STEMI, PMIR is a complication that may confound the prognosis. Post-PCI plasma BNP levels could be affected by myocardial ischaemia and inflammatory activation that follows reperfusion. Therefore, we should create an active management plan that attenuates myocardial ischaemia and inflammatory activation before and after primary PCI.

The present study had two main limitations. First, this study had a small sample size of PMIR patients. Second, a distribution of the infract-related artery and time from symptom onset to reperfusion was uneven because the clinical situation of each patient was different.

Conclusion

Elevated plasma BNP level was an independent predictor for PMIR. The optimal timing of plasma BNP measurement was in the early phase after the onset of STEMI. We should continue to use plasma BNP level to define its potential role in monitoring for PMIR.

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Epidemiological and clinical features, ultrasound findings and prognosis of right-sided infective endocarditis in a teaching hospital in Ouagadougou

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Abstract

Introduction: **Right-sided infective endocarditis is rare. It accounts about 5 to 10% of all infective endocarditis cases and is prevalent in patients with congenital heart disease, intravascular devices and drug addiction. Our study aimed to describe the epidemiological, clinical and echocardiographic characteristics of right-sided endocarditis and evaluate the prognosis after treatment.**

Methods: **From January 2010 to December 2011 we recruited all patients admitted to Yalgado Ouedraogo Teaching Hospital for infective endocarditis, and selected those who had a right-sided location. The Duke criteria were used for diagnosis. We analysed entry points and underlying heart disease. The causative organisms were tracked using blood sample cultures. Ultrasound characteristics were described, and treatment and prognosis were evaluated. Patients' follow up was conducted from recruitment to 30 June 2012.**

Results: **In the two-year period, 14 cases of right-sided infective endocarditis were recorded, including seven cases in children. They accounted for 29.1% of all infective endocarditis cases. The mean age was 25.5 ± 12.5 years (range 9–80 years). The venous route was implicated in 12 cases (85.7%). Blood cultures were positive in 11 patients. The bacteria isolated were *Streptococcus pneumonia* in six cases, *Staphylococcus aureus* in three and *Hemophilus influenza* in two cases. HIV status was positive in three patients. Underlying heart diseases were dominated by congenital heart disease in six cases and peripartal cardiomyopathy in four others. Vegetations were located in the right heart in only 11 cases. With antibiotic treatment, a lowering of temperature was shown within an average of 10 days of follow up. Two fatalities were reported.**

Conclusion: **This study showed that right-sided endocarditis is common in our clinical practice. This infection was prevalent in patients with congenital heart disease or peripartal cardiomyopathy in our context, and the venous route seemed to be the main entry point.**

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Infective endocarditis is a septicaemic state caused by transplantation of pathogens onto a previously healthy or injured endocardium or prosthetic valve. This definition encompasses infections developed in congenital heart disease and pacemaker probes.[1] The valve most commonly affected is the mitral valve in 41%, followed by the aortic valve in 38%.[2]

Right-sided endocarditis is rare and represents only 5 to 10% of infective endocarditis, according to a large case series.[3-7] It is found in patients with congenital heart disease or intravascular devices, and in drug addiction.[8,9]

The objectives of this study were to describe the epidemiological, clinical and echocardiographic characteristics of right-sided endocarditis, and assess its prognosis after treatment at the University Hospital of Ouagadougou (Burkina Faso).

Methods

We included consecutively, from 1 January 2010 to 31 December 2011, all patients admitted to the Yalgado Ouedraogo Teaching Hospital for diagnosis of infective or probable infective endocarditis, according to the Duke criteria.[10] Patients were recruited and admitted to the in-patient unit.

They were questioned to clarify the socio-demographic confounders (age, gender and occupation), disease history (heart disease, surgery, pacemaker, intravenous drug addiction, long-term catheter for dialysis or chemotherapy) and general signs. Physical examination collected information on the presence of signs of heart failure, modification of a pre-existing heart murmur, skin signs, Roth spots in the eye fundus examination, neurological signs, and entry points (dental, oto-rhino-laryngology, urogenital, venous access).

Para-clinical investigations focused on blood count, blood cultures, Addis count, retroviral serology, ECG, chest radiography and transthoracic echocardiography. We evaluated right ventricular systolic function by tricuspid annular plane systolic excursion (TAPSE), structural damage, and measured systolic pulmonary artery pressure using tricuspid regurgitation.

Treatment with antibiotics was administered according to the antibiogram for at least four to six weeks consecutively. We observed the evolution and possible complications during hospitalisation. On discharge from hospital, patients were

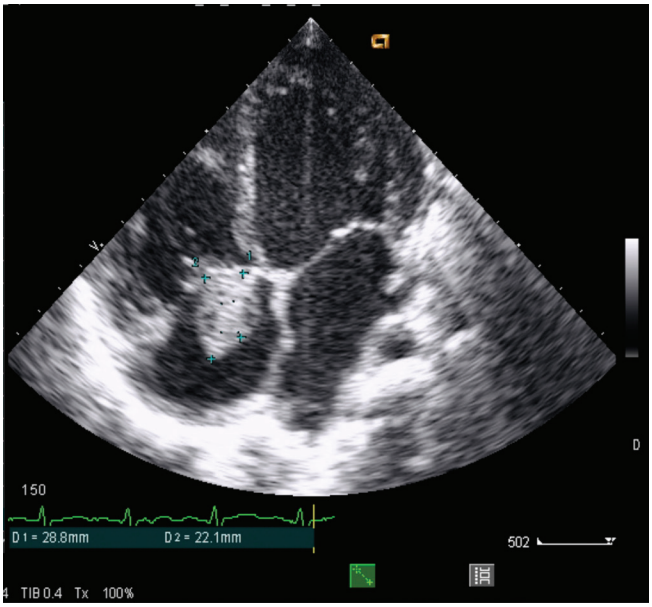

Fig. 1. Two-dimensional four-chamber echocardiogram showing large vegetations on the tricuspid valve.

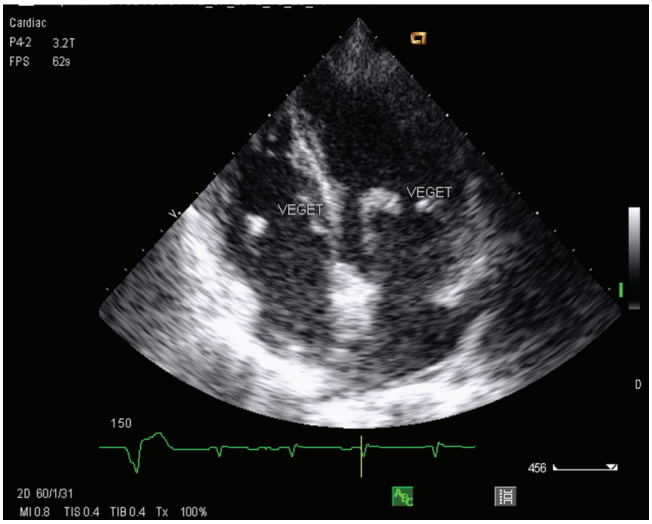

Fig. 2. Two-dimensional four-chamber echocardiogram showing vegetations on both tricuspid and mitral valves.

examined monthly as out-patients. During these follow-up visits, we were watching for fever, dyspnoea, and signs of right heart failure or inter-current illness.

Data analysis was done with SPSS. The results are expressed as numbers and percentage.

Results

During the study period, 48 patients with infective endocarditis were admitted to hospital, including 14 (29.1%) with right-sided endocarditis. The mean age was 25.5 ± 12.5 years (range from 9–80 years) and the gender ratio of women to men was 2.3. Children accounted for half of the right-sided endocarditis (seven cases).

A peripheral venous access had been performed in 12 patients in primary healthcare facilities and nine others had received inadequate antibiotic treatment. No case of drug addiction was recorded. Three patients were HIV positive while four were in the post-partum period.

Venous access was the entry point for bacteria in 12 patients (85.7%). The indications of venous access were malnutrition (five cases), childbirth (four cases), sickle cell crisis (two cases) and malaria (one case). In the other two cases, no entry point was found.

The clinical features included infectious syndrome in all patients, and right heart failure in nine cases. Tricuspid syndrome, consisting of fever associated with long-term lung damage (usually asymptomatic), anaemia and microscopic haematuria was found in six patients (42.8%). The diagnosis of infective endocarditis was based on the association of two major criteria in 12 patients and the association of one major criterion and three minor criteria in two other cases.

Blood sample cultures were positive in 11 patients, isolating *Streptococcus pneumonia* in six cases, *Staphylococcus aureus* in three cases and *Hemophilus influenzae* in two cases. Anaemia was common, as well as biological inflammatory syndrome (raised CRP, hyper-fibrinaemia and accelerated sedimentation rate) and leucocytosis.

The electrocardiogram revealed a left atrial enlargement in seven patients, left ventricular hypertrophy in six patients, right atrial and ventricular hypertrophy in three cases and atrial fibrillation in two children. Doppler echocardiography revealed vegetations in all patients. Vegetations were localised in the right heart only in 11 cases and on the tricuspid valve only in seven cases (Fig. 1). Otherwise vegetations were found both on the tricuspid and mitral valves in two cases (Fig. 2) and on the pulmonary valves in one case (Fig. 3). The average surface area of the vegetations was 2.9 ± 0.6 cm² (range 1.2–5.2). All patients had both tricuspid and pulmonary regurgitation.

Underlying heart diseases diagnosed by echocardiography Doppler are listed in Table 1.

Prior to the results of blood sample cultures, an early treatment with probabilistic antibiotics was made of a combination of a third-generation cephalosporin and an aminoglycoside, except in one case where the aminoglycoside was not introduced because of kidney failure. Once blood samples cultures had revealed a pathogen, the antibiotic treatment was then adjusted according to the antibiogram. Treatment was therefore adjusted in five patients. Heart failure was treated as appropriate.

The average hospital stay was 35 ± 7 days (range 24–49 days). The clinical course was marked by a lowering of temperature within an average treatment period of 10 days. Heart failure symptoms decreased as well. One fatality was reported in a child after 14 days of hospitalisation due to septic shock. After a mean

TABLE 1. DISTRIBUTION OF UNDERLYING HEART DISEASE IN PATIENTS WITH RIGHT-SIDED HEART ENDOCARDITIS AT THE YALGADO OUEDRAOGO UNIVERSITY HOSPITAL FROM JANUARY 2010 TO DECEMBER 2011 (*n* = 14)

Underlying heart disease	*Number*	*Percentage*
Peripartal cardiomyopathy	4	28.6
Dilated cardiomyopathy	2	14.3
Ventricular septal defect	2	14.3
Pulmonary stenosis + inter-atrial communication	2	14.3
Tetralogy of Fallot	1	7.1
Restrictive ventricular septal defect + ductus arteriosus	1	7.1
No heart disease found	2	14.3
Total	14	100

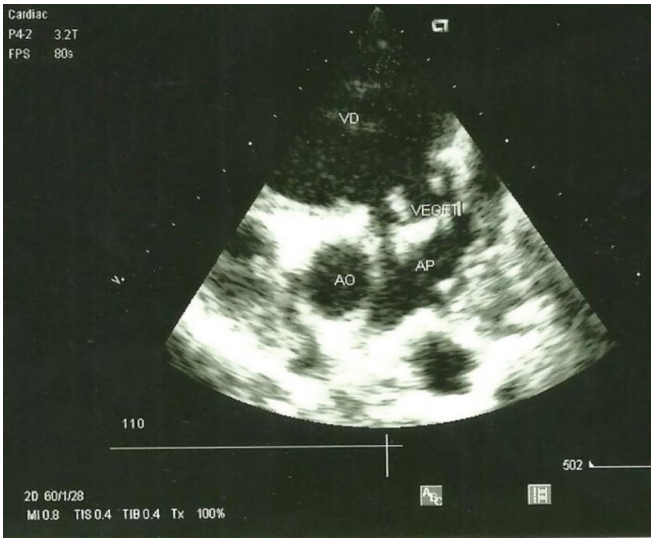

Fig. 3. Two-dimensional echocardiography, parasternal short-axis view showing vegetations on the pulmonary valves and pulmonary artery trunk.

follow-up period of 15.5 ± 6.8 months (range 6–30 months), a relapse occurred in two patients. Severe right heart failure was seen in three cases and one fatality was reported.

Discussion

Right-sided location during infective endocarditis is rare. It accounts for 5–10% of cases of endocarditis, according to the literature.[2-6] Right-sided endocarditis is most often reported in Africa, in very few cases. For instance, Ndiaye *et al*. in Sénégal[11] and Compaoré *et al*. in Moroco[12] reported six cases each. In South Africa, Naidoo *et al*. reported 15 cases.[13] We reported 14 cases, which represented 29.1% of all infective endocarditis during the study period.

Right-sided endocarditis is most often described in drug addicts and in iatrogenic infections (catheter, post-surgery) where venous access is the point of entry for the bacteria. In fact, about 80% of tricuspid endocarditis is found in drug addicts.[14]

In our study, venous access was implicated in 85.7% of cases. Immunosuppression, which is a risk factor for right-sided endocarditis,[15,16] was found in three patients in our cohort. In terms of aetiology, the microorganism most frequently isolated was *Staphylococcus aureus.*[17]

The clinical feature is almost invariably represented by the infectious syndrome. In some cases tricuspid syndrome can be found. This is a long-term fever associated with pneumonia (usually asymptomatic), anaemia and microscopic haematuria, as described by Nandakumar and Raju.[18] Six cases were identified in our series.

The main diagnostic tool in our study was echocardiography Doppler, by highlighting vegetations on the valves. Blood sample cultures were positive in 78.5% of cases.

Treatment of infective endocarditis is based on massive synergic long-term antibiotic therapy. The outcome is usually favourable.[17,19,20] The prognosis of right-sided endocarditis is usually excellent with medical treatment.[17] Complications are most often haemodynamic. They depend on the degree of valvular damage but also on underlying heart disease. Two cases of death were recorded in our study because of septic shock.

Conclusion

This study shows that right-sided endocarditis is common in our practice. This infection is prevalent in patients with congenital heart disease or peripartum cardiomyopathy. The entry point for microorganisms is almost exclusively the intravenous route. Blood cultures can in most cases identify the bacterium. These findings require health workers to pay more attention to the maintenance of venous access in patients receiving intravenous treatment.

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Maternal imbalance between pro-angiogenic and anti-angiogenic factors in HIV-infected women with pre-eclampsia

NALINI GOVENDER, THAJASVARIE NAICKER, JAGIDESA MOODLEY

Abstract

Angiogenic imbalance contributes to the development of pre-eclampsia. We evaluated the protein expression of the pro-angiogenic placental growth factor (PlGF) and transforming growth factor beta 1 (TGF-β_1) compared with the anti-angiogenic soluble fms-like tyrosine kinase receptor (sFlt1) and soluble endoglin (sEng) in HIV-infected normotensive and pre-eclamptic pregnancies.

Blood was obtained from 110 pregnant women, enrolled in four groups, namely, HIV-negative normotensives (27); HIV-positive normotensives (31); HIV-negative pre-eclamptics (27) and HIV-positive pre-eclamptics (25), and was used to measure PlGF, TGF-β_1, sFlt1 and sEng levels.

Increased sFlt1 and sEng levels were associated with the pre-eclamptics (HIV negative and positive) compared with their counterparts. Decreased PlGF levels were observed between the HIV-negative pre-eclamptics versus HIV-negative normotensives, but levels differed significantly (p = 0.02) among the normotensives (HIV negative and positive). TGF-β_1 remained unchanged across all groups. Higher sEng/TGF-β_1 ratios were associated with the pre-eclamptics (HIV negative and positive) compared with their counterparts. This study demonstrated increased sFlt1 and sEng levels in pre-eclamptic compared with normotensive pregnancies, irrespective of the HIV status.

Keywords: sFlt1, pre-eclampsia, anti-angiogenic factors, HIV

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Pre-eclampsia, a clinical syndrome unique to human pregnancy is characterised by new-onset hypertension and proteinuria, which present after the 20th week of gestation.[1-4] Although several studies in the last few decades have investigated the pathogenesis of this disorder, limited progress has been made in establishing the exact cause.[5,6]

Currently, pre-eclampsia is reported to be a two-stage disorder, namely, a pre-clinical/asymptomatic, and a clinical stage.[2,7] The first stage is characterised by abnormal placentation leading to a hypoxic placenta, oxidative stress and immune dysregulation, while the second stage is characterised by the placental discharge of soluble factors, such as sFlt1 and sEng into the maternal circulation, resulting in widespread endothelial dysfunction and the clinical syndrome of hypertension, proteinuria, intrauterine growth restriction (IUGR) and thrombocytopenia.[2,7-10]

Both pre-eclampsia and HIV infection are common conditions in sub-Saharan Africa and major causes of maternal deaths.[11] Recent studies have reported that the persistent infection of HIV-infected individuals contributes to the development of chronic arterial injury and subsequent endothelial damage, atherosclerosis and thrombosis.[12] Furthermore, untreated HIV-infected patients may be prone to endothelial dysfunction.[12] HIV infection also seems to affect the mechanisms implicated in the aetiology of pre-eclampsia and IUGR.

Normal pregnancy is characterised by an altered immune sensitivity, thereby allowing maternal resistance against any infection and foetal tolerance, while pre-eclampsia is a hyper-active immune response.[13,14] It is plausible that the immune insufficiency stimulated by HIV together with the normal immune changes of pregnancy may reduce a predisposition to the immune hyper-reactivity that is associated with pre-eclampsia.[15-17] Therefore it is not surprising that some reports have shown that a reduced rate of pre-eclampsia prevails among untreated HIV-infected patients in comparison with those on highly active antiretroviral therapy (HAART).[14,18]

The administration of HAART is reported to enhance maternal immune reconstitution by re-establishing the mother's immune response to foetal antigens, and consequently making the woman susceptible to the development of pre-eclampsia.[14] Conflicting reports however, have created uncertainty as to whether HIV-infected pregnant women on HAART have lower rates of pre-eclampsia.[17-19] This uncertainty may impact on both maternal and perinatal morbidity and mortality in a geographical region with a high prevalence of HIV.

Angiogenic biomarkers have been suggested for the early detection of pre-eclampsia in high-income countries, despite the lack of robust evidence for their use.[4,17] Therefore, this study set out to examine the role of pro- and anti-angiogenic factors in the aetiology of pre-eclampsia in a setting of high rates of HIV infection.

Methods

Institutional ethical and regulatory approvals were obtained. Clinical characteristics such as maternal and gestational age, parity, maternal, baby and placental weight, and blood pressure were collected during antenatal recruitment.

Venous blood samples were collected from 110 pregnant black African women at term attending a tertiary maternity unit in Durban, KwaZulu-Natal, South Africa. All blood samples

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were centrifuged within two hours at 3 500 rpm for 10 min at 4°C. Serum aliquots were then carefully transferred into new tubes and stored at –70°C until analysis. Enzyme-linked immunoassays for PlGF (1:2), TGF-β_1 (1:40), sFlt1 (1:5) and sEng (1:5) were performed in triplicate according to the manufacturer's instructions (R&D Systems, Minneapolis, MN).

Fifty-two of the blood samples were obtained from pre-eclamptics and 58 from normotensive pregnant women. These groups were further subdivided into HIV-negative and HIV-positive sub-groups.

Inclusion criteria for pre-eclampsia were persistent systolic blood pressure 140 mmHg and diastolic blood pressure 90 mmHg, taken at least six hours apart, after 20 weeks' gestation in a previously normotensive patient. Proteinuria was defined as urine protein concentration of ≥ 300 mg/dl or 1+ on a urine dipstick in at least two random specimens collected at least four hours apart.

Exclusion criteria for all groups was chorio-amnionitis, chronic hypertension, eclampsia and abruptio placentae; intrauterine death, pre-gestational diabetes, gestational diabetes and chronic renal disease; systemic lupus erythematous, sickle cell disease and anti-phospholipid antibody syndrome; thyroid disease, cardiac disease and active asthma requiring medication during pregnancy and pre-existing seizure disorders.

Statistical analysis

Inter-group analysis was conducted using the non-parametric Kruskal-Wallis test. Descriptive statistics were utilised and outcome variables are presented as median (interquartile range). Where differences were found in the Kruskal-Wallis test, Dunn's *post hoc* test was used for multiple comparisons. A probability level of $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using GraphPad Prism® version 5.01.

Results

Clinical characteristics for the pre-eclamptic and normotensive participants ($n = 110$) were divided into HIV-positive ($n = 56$) and HIV-negative groups ($n = 54$), respectively, namely, (1) HIV-negative normotensive (N–): BP ≤ 120/80 mmHg ($n = 27$); (2) HIV-positive normotensive (N+): BP ≤ 120/80 mmHg; CD_4 < 200 cells/µl ($n = 31$); (3) HIV-negative pre-eclamptic (P–): BP 140/90 mmHg ($n = 27$) and (4) HIV-positive pre-eclamptic (P+): BP 140/90 mmHg; CD_4 < 200 cells/µl ($n = 25$) (Table 1).

A significant difference was detected for maternal and gestational age, parity, maternal and placental weight, and systolic and diastolic blood pressure ($p < 0.05$) between the four groups (Kruskal-Wallis test, Table 1). Mean maternal age ranged between 23 and 30 years while the mean gestational age ranged between 37 and 39 weeks (Table 1).

For maternal weight, the Kruskal-Wallis test showed an overall significance ($p < 0.05$). The Dunn's multiple comparison tests identified a significant difference between only the HIV-positive pre-eclamptic and the HIV-negative normotensive pregnant women ($p = 0.0321$; Table 1). However, for placental weight (Table 1), a significant difference was evident between the HIV-positive pre-eclamptic and HIV-negative normotensive pregnant women ($p < 0.0001$), the HIV-negative pre-eclamptic and HIV-negative normotensive pregnant women ($p < 0.0001$) and the HIV-positive normotensive and HIV-negative normotensive pregnant women ($p < 0.0001$; Table 1).

For systolic blood pressure (Table 1), a significant difference was evident between the HIV-positive pre-eclamptic and HIV-negative normotensive pregnant women ($p < 0.0001$), the HIV-positive pre-eclamptic and the HIV-positive normotensive pregnant women ($p < 0.0001$), the HIV-negative pre-eclamptic and the HIV-negative normotensive pregnant women ($p < 0.0001$) and the HIV-negative pre-eclamptic and HIV-positive normotensive pregnant women ($p < 0.0001$). A similar pattern was observed for diastolic blood pressure, as indicated in Table 1.

Pro-angiogenic and anti-angiogenic factors

Serum concentrations for all evaluated pro-angiogenic (PlGF and TGF-β_1) and anti-angiogenic (sFlt1 and sEng) factors varied (Table 2, Figs 1a–d and 2a–c). A significant difference was observed for sFlt1, sEng and PlGF ($p < 0.05$) between the groups (Figs 1a–d). For sFlt1, the Kruskal-Wallis test showed an overall significance ($p < 0.05$). The Dunn's multiple comparison test revealed a significant difference between HIV-negative pre-eclamptic and HIV-negative normotensive pregnant women ($p = 0.0061$), and HIV-negative pre-eclamptic and HIV-positive normotensive pregnant women ($p = 0.0061$).

A significant difference for sEng (Table 2, Fig. 1) was evident between HIV-positive pre-eclamptic and HIV-positive normotensive pregnant women ($p = 0.0017$), and HIV-negative pre-eclamptic and HIV-positive normotensive pregnant women ($p = 0.0017$). Likewise for PlGF, a significant difference was found between the HIV-negative pre-eclamptic and HIV-negative normotensive pregnant women ($p = 0.021$), and the HIV-negative

TABLE 1. DEMOGRAPHIC AND CLINICAL PROFILE OF PATIENTS RECRUITED FOR IMMUNOASSAYS

	Normotensive pregnant women (N–)	*HIV normotensive pregnant women (N+)*	*Pre-eclamptic pregnant women (P–)*	*HIV pre-eclamptic pregnant women (P+)*	p-*value*
Number	27	31	27	25	
Age (years)	24 (21–26)	27 (24–30)	25 (20–32)	32 (25.5–34)	0.0009*
Gestational age (weeks)	38 (38–39)	39 (38–40)	38 (37–40)	38 (36–38)	0.0026*
Parity	0 (0–1)*	1 (1–2)	1 (0–1)	1 (0.5–3)	0.0174*
Maternal weight (kg)	66 (59–74)	74 (65–82)	75 (65–96)	82 (64–106)	0.0321*
Birth weight (kg)	3.2 (3–3.4)	3.4 (3–3.7)	3.2 (2.6–3.8)	2.9 (2.7–3.4)	ns
Placental weight (g)	360 (300–400)	470 (380–500)	480 (430–510)	480 (380–515)	< 0.0001*
Systolic BP (mmHg)	110 (108–115)	112 (107–120)	154 (150–162)	150 (145.5–159)	< 0.0001*
Diastolic BP (mmHg)	70 (67–73)	70 (67–74)	94 (90–104)	9 6 (87–99.5)	< 0.0001*

Medians (range) are presented; Kruskal-Wallis test and the *post hoc* Dunns multiple comparison test was used for statistical analysis, $n = 110$. *$p < 0.05$

TABLE 2. COMPARISON OF PRO-ANGIOGENIC AND ANTI-ANGIOGENIC FACTORS OF MATERNAL SERUM ACROSS STUDY GROUPS

	Normotensive pregnant women (N–)	*HIV normotensive pregnant women (N+)*	*Pre-eclamptic pregnant women (P–)*	*HIV pre-eclamptic pregnant women (P+)*	*p-value*
Number	27	31	27	25	
sFlt-1(pg/ml)	10249 (6308–13708)	8578 (5898–13769)	15617 (11257–20641)	11494 (8203–15784)	0.006*
sEng (ng/ml)	13.14 (9.6–17.92)	10.4 (7.3–16)	20.5 (8.5–29)	23 (11.8–52.5)	0.002*
PlGF (pg/ml)	488.6 (183.9–848.3)	207.1 (102.6–358.6)	202.2 (47.9–490.4)	229.3 (74.3–615.9)	0.021*
TGF-β1 (pg/ml)	27640 (22308–35771)	31164 (26916–37474)	32652 (27295–39328)	32301 (24983–37355)	ns
sEng/TGF-β1 (pg/ml)	0.48 (0.33–0.6)	0.32 (0.2–0.45)	0.62 (0.38–0.95)	0.59 (0.38–1.5)	0.002*
sFlt-1/PlGF (pg/ml)	21.4 (7.2–50.8)	41.6 (14.5–140.7)	66.5 (28.3–136.9)	37.3 (14.8–106.2)	ns
sFlt1+sEng/ PlGF (pg/ml)	12392 (8792–15700)	9422 (7014–16914)	12988 (6859–17276)	10772 (8345–13527)	ns

Medians (range) are presented; Kruskal-Wallis test and the *post hoc* Dunns multiple comparison test was used for statistical analysis, $n = 110$. *$p < 0.05$; non-significant (ns).

normotensive and HIV-positive normotensive pregnant women ($p = 0.021$). However, TGF-β_1 did not differ significantly between groups ($p = 0.359$; Fig. 1).

Anti-angiogenic ratio analyses revealed a significant difference only for sEng/TGF-β_1 ratios ($p < 0.05$, Table 2, Fig. 2a). Accordingly, the Dunn's multiple comparison test revealed a significant difference for both HIV-positive pre-eclamptic and HIV-positive normotensive pregnant women ($p = 0.002$), and HIV-negative pre-eclamptic and HIV-positive normotensive pregnant women ($p = 0.002$).

Discussion

Since placental delivery is the only cure for pre-eclampsia, its clinical management is dependent on gestational age and disease severity. In our study, gestational age and placental weight varied among the study groups. The pre-eclamptic groups (HIV positive and negative) delivered at a slightly earlier gestational period compared with the normotensive groups.

Our data revealed that placental weights for the pre-eclamptic groups were greater than the normotensive groups. This is surprising as one would have expected the placental weights

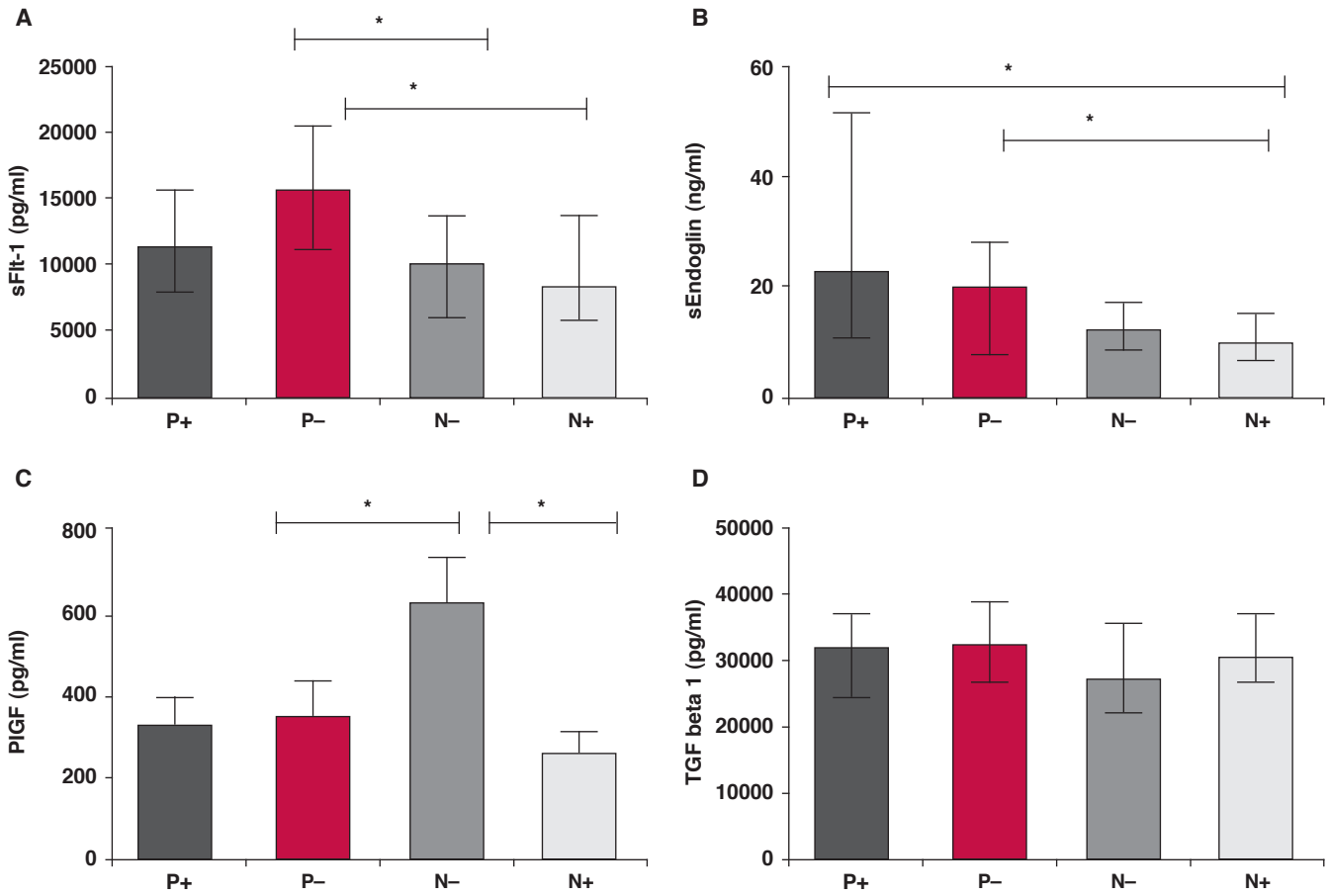

Fig.1. Pro-angiogenic and anti-angiogenic serum concentrations (medians with interquartile range). (A) sFlt1 (pg/ml), (B) sEng (ng/ml), (C) PlGF (pg/ml) and (D) TGF beta 1 (pg/ml); HIV-positive pre-eclamptic (P+); HIV-negative pre-eclamptic (P–); HIV-negative normotensive (N–) and HIV-positive normotensive (N+).

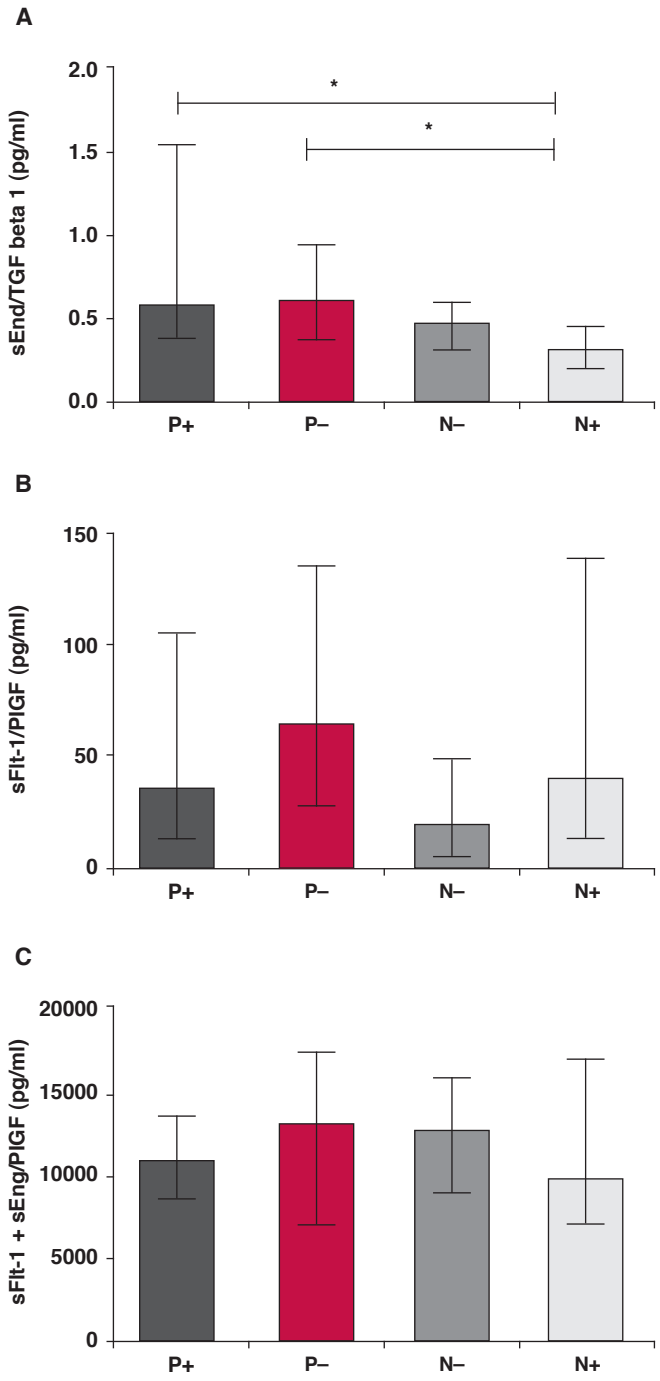

Fig. 2. Anti-angiogenic ratio of serum concentrations (medians with interquartile range). (A) sEng/TGF-β1, (B) sFlt1/PlGF and (C) (sFlt1 + sEng)/PlGF; HIV-positive pre-eclamptic (P+); HIV-negative pre-eclamptic (P–); HIV-negative normotensive (N–) and HIV-positive normotensive (N+).

in pre-eclamptics to be lower in view of the fact that the pre-eclamptics delivered at a lesser gestational age and the fact that pre-eclampsia is associated with IUGR. Alternatively, this higher placental weight may be attributed to the late onset of pre-eclampsia.

Although we did not correlate foetal growth with gestational age following delivery, there is circumstantial evidence that women with gestational hypertension and mild pre-eclampsia tend to have slightly bigger babies and larger placental masses than their normotensive counterparts at birth. It is plausible that mild increases in blood pressure could cause a concomitant increase in placental perfusion pressure and increased oxygen supply, resulting in increased placental size.

However, a recent epidemiological analysis conducted by Eskild and Vatten (2010) reported conflicting data with regard to placental weight.[20] Pre-eclampsia is hypothesised to be due to placental dysfunction, however these investigators have suggested that placental weight may not be a risk indicator for the placental dysfunction evident in pre-eclampsia. In addition, the placenta is identified as the major angiogenic contributor, and that the imbalance evident in pre-eclampsia may be associated with placental hypoxia.[20]

Therefore the pre-eclamptic placenta is involved with the cause of the disease and is implicated in the production of elevated levels of sFlt1 and sEng.[2,21-23] This elevation is believed to disrupt the balance of the pro-angiogenic factors, thereby decreasing their bioavailability, with the subsequent vascular maladaptation of pre-eclampsia.

Our study further demonstrated variations between the pro-angiogenic (PlGF and TGF-β_1) and anti-angiogenic factors (sFlt1 and sEng) that occurred in pre-eclamptic (HIV negative and positive) and normotensive (HIV negative and positive) pregnancies, lending credence to the anti-angiogenic theory of pre-eclampsia. To our knowledge, there are no available data that explore the relationship of HIV with circulating pro-angiogenic and anti-angiogenic factors in pre-eclampsia.

VEGF is recognised as a powerful endothelial-specific mitogen and its significant role in angiogenesis is well documented.[24-26] It is functional through the two high-affinity receptor tyrosine kinases VEGFR1 (Flt1) and VEGFR2 (Flk1). PlGF is also a member of the VEGF family, which binds to Flt1, thereby supplementing the pro-angiogenic effects of VEGF.[24-26] However, a soluble isoform and a splice variant of Flt1 have been identified as sFlt, which contains a ligand-binding domain but lacks a trans-membrane and cytoplasmic domain.[27] Karumanchi and co-workers further demonstrated an excess production of sFlt1 by the pre-eclamptic placental trophoblasts and subsequent discharge into the maternal circulation, implicating it as a key role player in the aetiology of this maternal syndrome.[27]

Transforming growth factor-beta (TGF-β_1), comprising three isoforms, is important for the development of the embryo, inflammation repair, and angiogenesis.[28] TGF-β_1, an isoform expressed copiously in trophoblasts and endothelial cells, functions as an apoptotic and proliferative mediator of vascular endothelial cells, immunosuppression and production of the cellular matrix.[29] Furthermore, TGF-β_1 contributes to the normal placentation through the control of trophoblast invasion.[30]

However, in pre-eclampsia it affects trophoblast cell migration and influences spiral artery conversion by activating gene transcription and increasing the synthesis of matrix proteins.[31] It also decreases pericellular proteolysis by decreased synthesis of proteolytic enzymes such as the serine and matrix metalloproteinases (MMPs), and increases the synthesis of tissue inhibitors (TIMPs), thereby modifying the repertoire of cell adhesion receptors such as the integrins.[31] In the current study we were unable to demonstrate any significant difference for TGF-β_1 between the groups.

Endoglin (Eng), a co-receptor for both TGF-β_1 and TGF-β_3,

is highly expressed in syncytiotrophoblasts and endothelial cells.[29,33] It is identified as a pro-angiogenic factor that regulates vascular remodelling and homeostasis via the endothelial nitric oxide synthase pathway.[29,32-34] In contrast, sEng prevents the signalling pathway of TGF-β_1 and the endothelial stimulation of TGF-β_1-mediated nitric oxide synthase pathway, thereby obstructing endothelial and capillary development.[31,35]

Consequently, the anti-angiogenic effects of sEng evident in pre-eclampsia occur via its interaction with TGF-β_1, resulting in the inhibition of the endothelial attachment of TGF-β_1 and the subsequent loss of the endothelial pro-angiogenic and vasodilatory effects of TGF-β_1.[22,31,34,35] Therefore the clinical significance of elevated levels of sFlt1 and sEng and their role as powerful anti-angiogenic factors through their interaction with the circulating levels of VEGF, PlGF and TGF-β_1, respectively, is well established.

Our study confirmed previous reports of elevated serum levels of sFlt1 and sEng in pre-eclamptic compared with normotensive groups.[10,27,36] In addition, we showed a significant difference for sFlt1, sEng and PlGF between all groups. Furthermore, sFlt1 and sEng were higher in the pre-eclamptic (HIV negative and positive) compared with normotensive pregnancies (HIV negative and positive).

In our study, the HIV-negative normotensive pregnant women had higher levels of PlGF compared with both pre-eclamptic groups, confirming previous reports.[21,27,37] PlGF was reduced in the HIV-positive normotensive versus both the HIV-negative and HIV-positive pre-eclamptic groups. Pre-eclampsia is associated with decreased levels of PlGF, with the concurrent increase of sFlt1. This trend was observed in our study among the HIV-negative normotensive versus the pre-eclamptic groups. Unexpectedly, this trend was reversed in the HIV-positive normotensive group. It is therefore possible to assume that the immune insufficiency stimulated by HIV infection reduced a predisposition to immune hyper-reactivity, forestalling the development of pre-eclampsia. Moreover, there was a significantly higher difference between the HIV-negative and the HIV-positive normotensive groups.

The sFlt1/PlGF ratio has diagnostic predictor test value for pre-eclampsia.[38,39] It is therefore evident that the clinical significance of the sFlt1/PlGF ratio, which represents the anti-angiogenic role in pre-eclampsia, characterises the stability between sFlt1 and PlGF. Our results showed a lower sFlt1 and sFlt1/PlGF ratio in the HIV-positive pre-eclamptic compared with the HIV-negative pre-eclamptic groups, indicative of an apparent trend towards a diagnostic value. The imbalance that occurs in pre-eclampsia may be attributed to the immunological nature of the disease, however this requires further investigation.

Unlike sFlt1 in the HIV-positive pre-eclamptics, sEng varied compared with the HIV-negative pre-eclamptic groups. Furthermore, when combined as an anti-angiogenic ratio (sEng/TGF-β_1), a significantly lower difference was evident between the control and pre-eclamptic groups. The HIV-negative and HIV-positive pre-eclamptic pregnant females showed higher sEng/TGF-β_1 ratios compared with both normotensive groups.

The HIV-positive pre-eclamptics showed a higher ratio compared with the HIV-negative pre-eclamptic groups, while the average ratios of the HIV-positive normotensives were lower than the HIV-negative normotensive pregnant women. These results, albeit in term pregnancies, suggest that these ratios may have a clinical significance during early pregnancy as a predictor test for the development of pre-eclampsia.

An elevation of plasma and platelet-depleted plasma levels of TGF-β_1 in pre-eclampsia compared with normotensive pregnancy has previously been reported.[40] Our study, however, demonstrated no significant differences in serum TGF-β_1 levels, with a concomitant significance of sEng/TGF-β_1 ratio for the HIV-positive pre-eclamptics versus HIV-positive normotensives, and the HIV-negative pre-eclamptics versus HIV-positive normotensives.

Our results were similar to, albeit higher than, that observed by Huber *et al.* (2002), showing no significant difference in TGF-β_1 expression between the pre-eclamptic and normotensive groups.[41] Noteworthy, the analyses of sEng/TGF-β_1 ratio in our study implicated a role for TGF-β_1 in the pathogenesis of pre-eclampsia. However, a limitation to our study was the relatively small sample size, and this requires further investigation.

Conclusion

Our study demonstrated elevations in both sFlt1 and sEng levels in pre-eclamptic compared with normotensive pregnancies, irrespective of the HIV status. Quantification of serum pro-angiogenic/anti-angiogenic factors in HIV-associated pre-eclampsia is novel.

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Prevalence and determinants of hypertension and associated cardiovascular risk factors: data from a population-based, cross-sectional survey in Saint Louis, Senegal

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Abstract

Background: **The incidence of cardiovascular disease is growing worldwide and this is of major public health concern. In sub-Saharan Africa, there is a lack of epidemiological data on the prevalence and distribution of risk factors of cardiovascular disease. This study aimed at assessing the prevalence of hypertension and other cardiovascular risk factors among an urban Senegalese population.**

Methods**: Using an adaptation of the WHO STEPwise approach to chronic disease risk-factor surveillance, we conducted a population-based, cross-sectional survey from 3 to 30 May 2010 on 1 424 participants aged over 15 years. Socio-demographic and behavioural risk factors were collected in step 1. Physical anthropometric measurements and blood pressure were documented in step 2. Blood tests (cholesterol, fasting blood glucose, and creatinine levels) were carried out in step 3.**

Results**: The prevalence of hypertension was 46% (95% CI: 43.4–48%), with a higher prevalence in females (47.9%) than males (41.7%) ($p = 0.015$), and 50% of these hypertensive were previously undiagnosed. Mean age was 53.6 years (SD: 15.8). In known cases of hypertension, the average length of its evolution was 6 years 9 months (range 1 month to 60 years). Hypertension was significantly associated with age ($p = 0.001$), socio-professional category ($p = 0.003$), dyslipidaemia ($p < 0.001$), obesity ($p < 0.001$), physical inactivity ($p < 0.001$), diabetes ($p < 0.001$) and stroke ($p < 0.001$).**

Conclusion**: We found a high prevalence of hypertension and other cardiovascular risk factors in this population. There is need of a specific programme for the management and prevention of cardiovascular disease in this population.**

Keywords: hypertension, cardiovascular, Africa, risk factors, Senegal

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Hypertension (HTN) remains a major public health concern worldwide and particularly in sub-Saharan Africa.[1-3] The overall prevalence of HTN worldwide is estimated to be 30% and the attributable mortality is ~30%. Lawes *et al*. reported that overall, about 80% of the attributable burden occurred in low- and middle-income economies, and over half occurred in people aged 45–69 years.[4]

In sub-Saharan Africa, the prevalence of HTN is estimated to vary between 15 and 33%.[1] HTN is usually associated with other cardiovascular risk factors such as diabetes, dyslipidaemia and obesity.[5] In Senegal, there is a lack of population-based epidemiological data on HTN and cardiovascular risk factors. Our study aimed at assessing the prevalence and deteminants of HTN and associated cardiovascular risk factors among an urban population in Senegal (Saint Louis).

Methods

This study was a population-based, cross-sectional survey conducted in the city of Saint Louis (north Senegal, 250 km from the capital Dakar). It population is 190 000 inhabitants (2008 estimate) and the number of subjects over 15 years is estimated at 110 000.

Data were collected in three steps;[6] step 1 comprised using a questionnaire to collect demographic and lifestyle data; step 2 involved measurements of height, weight, blood pressure, waist and hip circumference; and step 3 included laboratory

(biochemistry) investigations. Data presented in this publication are related only to hypertension.

A list of the districts in the city was used for sampling. Each district was divided into squares and each square was subdivided into concessions (a group of households). A list of all concessions was obtained from the regional statistics office. This list was used as a sampling frame for the random selection of squares.

In each square, concessions to be visited were randomly selected and inside the concession, a household was also randomly selected. In each household, all the persons matching the selection criteria were invited to participate in the study. One hundred and twenty households were randomly selected, giving a total of 1 424 participants; 32 sets of data were not been analysed because of missing biological and/or clinical data.

Eligible criteria were age ≥ 15 years and being a resident of Saint Louis. Formal written consent was obtained. Non-consenting patients and pregnant women were not included.

Participants were involved in the survey for one day. Those with abnormal physical or laboratory findings were counselled and referred to the regional hospital as defined by the National Health reference system. Interviews, body measurements and laboratory tests were performed by nurses and clinical officers.

The survey questionnaire consisted of socio-demographic (age, gender, education, marital status), lifestyle variables (fruit and legume consumption, exposure to tobacco and alcohol, and physical activity), and medical and health history.

Physical body measurements included blood pressure (BP), height, weight, and waist circumference. Blood pressure measurements were taken using an electronic digital blood pressure machine (OMRON® M6). Three BP measurements were performed on both arms, in a seated position, legs uncrossed, after a five- to 10-minute rest. The highest BP value was recorded.

Waist circumference was measured in centimeters using a tape measure, and the measurement was made at the mid-axillary line, midway between the last rib and the superior iliac crest. Height was measured with the participant standing upright against a wall on which a height mark was made. Weight measurements were taken on a pre-calibrated weighing scale (Seca 750). Participants were weighed dressed in light clothing and barefoot.

Blood samples were analysed in a single laboratory using an automate Reflotron- Plus®. Cholesterol [total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL)], triglyceride, fasting blood glucose, uric acid and creatinine levels were analysed.

Hypertension was defined as a systolic BP ≥ 140 mmHg or a diastolic BP ≥ 90 mmHg, or a documented medical history of antihypertensive treatment.[7] Obesity was defined as body mass index (BMI) ≥ 30.0 kg/m^2, and overweight by a BMI > 25 but < 30 kg/m^2.

Diabetes mellitus was defined as two fasting blood glucose levels > 1.26 g/l and/or a documented medical history of diabetes or diabetes treatment. The threshold for normal values were < 2 g/l for total cholesterol, < 1.6 g/l for LDL cholesterol, > 0.4 g/l for HDL cholesterol, and < 1.5 g/l for fasting triglycerides.

Physical inactivity was defined as the absence of daily physical activity or the presence of physical activity lasting less at 150 minutes per week. Abdominal obesity was defined according to NCEP, with a waist circumference greater than 102 cm in men and 88 cm in women.

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

Statistical analysis

Data recorded in the standard questionnaire were double checked by external monitor and double-entered using Epi Data software. Entered data were cleaned and analysed by an experienced biostatistician using Epi info version 3.5.1 software.

Binary variables were described by their proportion and continuous variables by means and standard deviation (SD). Pearson and Yates (when appropriate) chi-square test were used for the comparison of qualitative variables and Student's *t*-test for the comparison of quantitative variables between groups. A logistic regression model was built with variables associated with hypertension. Age and gender were forced into the final model. The results were statistically significant if $p < 0.05$.

Results

We recruited 1 424 participants (983 female, 69%). Mean age was 43.4 years (SD: 17.8), (range 15–96 years); 70.8% were < 55 years and 87.5% were < 65 years. Fig. 1 shows the distribution of the population by age. Table 1 shows the characteristics of the enrolled population and Table 2 shows the prevalence of various cardiovascular risk factors.

Six hundred and fifty-five participants had HTN, giving a prevalence of 46.0% (95% confidence interval: 43.4–48.6%). Among these 655 cases, 327 (50%) were previously undiagnosed. HTN was more frequent in females [47.9% (44.8–51.1%)] than in males [41.7% (37.1–46.5%), $p = 0.015$, OR = 1.29 (1.02–1.62)]. The mean age was significantly higher in the hypertensive participants (53.6, SD: 15.8 years) than in non-hypertensive participants (34.7 years, SD: 14.5, $p < 0.001$). The prevalence of HTN increased with age ($p = 0.001$) (Fig. 2). Mean duration of HTN was 6.9 years (range: 1 month – 60 years).

Among HTN participants, mean systolic BP was 136 mmHg and mean diastolic BP 88 mmHg. Grade 1 HTN was more frequent (48%) than grade II (25%) and grade III (27%). HTN tended to be more frequent in participants who had primary school level education (42.1%) than in those who had higher levels of education (28.4%, $p = 0.18$). Table 3 shows the distribution of hypertension according to socio-professional category. There

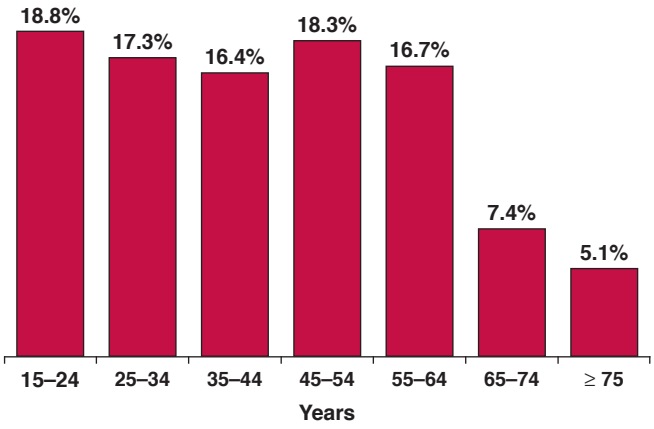

Fig. 1. Distribution of study population by age (*n* = 1 424).

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION (n = 1 424)

	Female	*Male*	*Total*	p
Sample size	983	441	1424	
Age (years), mean (SD)	44.2 (17.2)	41.7 (18.9)	43.4 (7.8)	0.016
Weight (kg), mean (SD)	71.7 (17.9)	67.6 (13.6)	70.5 (16.7)	< 0.001
Height (cm), mean (SD)	163.3 (8.3)	174.9 (8.5)	166 (9.9)	< 0.001
Waist circumference (cm), mean (SD)	87.4 (16.5)	81.2 (46.8)	84.6 (15.9)	0.0003
Systolic BP (mmHg), mean (SD)	131.1 (28.7)	131.9 (22.3)	131.2 (27.8)	0.893
Diastolic BP (mmHg), mean (SD)	86.7 (24.5)	82.4 (22.4)	85.4 (22.4)	0.0001
BMI (kg/m²), mean (SD)	27 (7.2)	22.1 (16.2)	25.5 (6.7)	< 0.001

SD: standard deviation

was a statistically significant relationship between hypertension and the different socio-professional categories, except for self-employed, privately employed and volunteer participants (p = 0.0031).

Diabetes was detected in 16.5% (13.8–19.6%) of the participants with HTN and in 5.2% (3.8–7.1%) of participants without HTN [p = 0.023, OR = 0.32 (0.21–0.47)]. Moreover, HTN was more frequent in participants with diabetes [73% (65.1–79.9%)] than in those without diabetes [43% (40.1–45.6%), p < 0.0001, OR = 3.59 (2.46–5.25)].

Other risk factors associated with HTN were dyslipidaemia in 71.1% (67.5–74.6%) of participants with HTN versus 59% (55.5–62.5%) in non-HTN participants (p < 0.001), physical inactivity [48.5% (43.9–52.1%) vs 40.2% (36.3–44.5%), p < 0.001] and abdominal obesity [47.3% (43.5–51.2%) vs 21.2% (18.4–24.3%), p < 0.001].

HTN was more frequent in the case of a past history of smoking (50.8%) (41.8–59.7%) than in passive exposure (44.8%) (40.9–48.8%) and cigarette users (33.7%) (23.7–44.9%). A medical history of stroke was more frequent in participants with HTN (2.7%) (1.7–4.4%) compared with those without HTN (0.5%) (0.2–1.4%) (p < 0.001). HTN was correlated with the creatinine level (p < 0.05) (Fig. 3). The mean clearance rate of creatinine gradually decreased with the duration of hypertension (Fig. 4) (p = 0.26).

Discussion

In order to gather data on the frequency of HTN and associated risk factors in urban Saint Louis residents, we carried out a population-based, cross-sectional survey with a methodology closed to the WHO STEPwise approach. We found a significant increase in the prevalence of HTN.

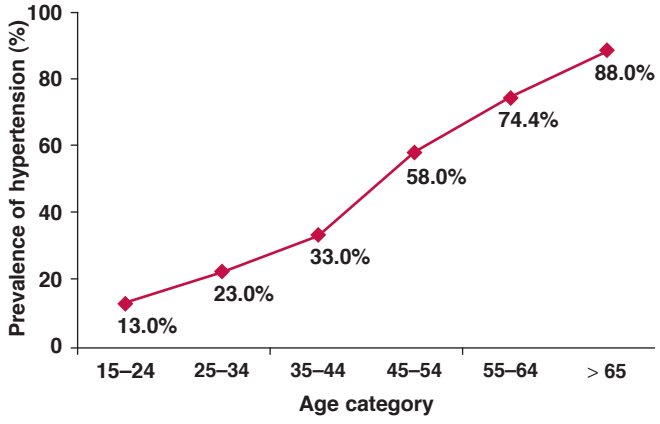

Fig. 2. Prevalence of hypertension by age (n = 655).

TABLE 2. PREVALENCE OF CARDIOVASCULAR RISK FACTORS IN THE STUDIED POPULATION (n = 1 424)

Risk factors	*Prevalence, % (95% CI)*
Hypertension	46 (43.4–48.6)
Abdominal obesity	33.2 (30.8–35.7)
Obesity (BMI > 30 kg/m²)	23 (18.1–28.2)
Tobacco smokers	5.8 (4.7–7.2)
Physical inactivity	44.4 (40.2–49)
Diabetes	10.4 (8.9–12.1)
Raised cholesterol (> 2 g/l)	36.3 (33.8–38.9)
Raised LDL cholesterol (> 1.6 g/l)	20.6 (18.5–22.8)
Low value of HDL cholesterol	41.9 (39.4–44.5)
Metabolic syndrome	15.8 (14–17.8)

BMI: body mass index, CI: confidence interval.

TABLE 3. PREVALENCE OF HYPERTENSION IN SOCIO-PROFESSIONAL CATEGORY

	Number	*Hypertension (%)*	p
Official	71	36.6	1
Private	72	25	0.13
Self employed	496	48.2	0.06
Volunteer	9	22.2	0.39
Housewife	528	50.9	0.023
Student	130	10	< 0.001
Unemployed	35	57.1	0.045
Retired	83	81.9	< 0.001

A previous study performed in the same region in 1970 found a prevalence of 4.9% in a rural population, whereas the prevalence was 7% in an urban population. Even though the methodology (HTN if BP ≥ 160/95 mmHg) in this study was not similar to ours, our results suggest a significant increase in the prevalence of HTN since 1970.[8] Moreover, Kane *et al*. in 1995 found a prevalence of 20.2% with a methodology very similar to ours.[5] In the sub-Saharan African region, two studies have reported a median prevalence of 28%, with a regional variation ranging from 15 to 38.6%.[1,9] Changes in lifestyle may be the major factor leading to this increasing prevalence of HTN and other cardiovascular risk factors.[9-11]

While we have not found significant associations between HTN and level of education, it should be noted that previous studies found such an association. The ENNS trial found than HTN was twice as frequent in people with a primary level of education than in those who had secondary or postgraduate levels of education. This difference was higher in women: the risk of HTN was four-fold higher in less-educated women than in those with higher levels of education.[2] The same observation was made in Brazzaville, Congo.[9]

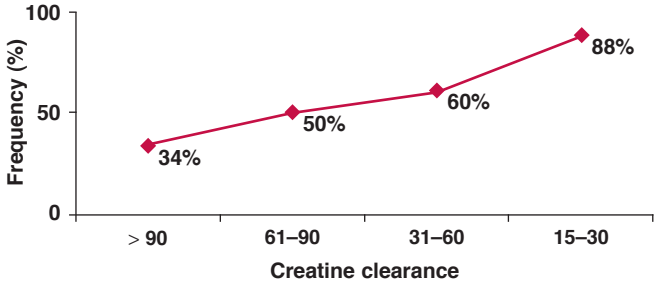

Fig. 3. Prevalence of hypertension by creatinine clearance rate (n = 655).

The association between HTN and low socio-econonomic conditions is well described in studies conducted in low-income countries. The lower the socio-economic income, the higher is the probability of having HTN.[12,13]

In our population sample, women were more represented than men. This could have been related to the observation that women were more likely to be at home at the time the study team visited than men, who were involved in economic activities outside the home. Additionally, men were more inclined to decline participation in the survey. This observation was noticed by other authors in this kind of population-based survey.[14]

We found a predominance of HTN in women. This observation was previously reported in the CONSTANT trial in Guadeloupe (37.3 vs 33%) and Tunisia (36 vs 25%).[12,13] This is in contradiction with the predominance of HTN found in males, reported in many epidemiological surveys.[2,14] Some authors have suggested that women are protected from HTN up to menopause.

In our study, obesity and inactivity were significantly more frequent in women than men, and females were older than males. This could explain the predominance of HTN in the women. We also noted a significantly higher diastolic blood pressure in women than in men, for which we did not find an explanation, except that the women may have had more risk factors.

Regarding other risk factors, we found that age correlated with the prevalence of HTN. This was previously noted in Algeria and France.[9,15] Obesity accounted for 11 to 25% of HTN and prevention studies have reported that a decrease of 1 kg of body weight led to a decrease of 1.1/0.9 mmHg in BP.[16-18] The meta-analysis of Whelton (54 randomised clinical trials) reported a decrease of 3.8/2.9 mmHg in people with regular aerobic physical activity; the highest decrease was found in hypertensive subjects (4.9/3.7 mmHg).[17]

Obesity and physical inactivity are known to be risk factors for the onset of diabetes, HTN and other cardiovascular diseases. The review of Sowers showed that HTN was twice as frequent in patients with diabetes than in those with normal glycaemia. Additionally, Sowers reported an increase in the risk of diabetes in HTN patients compared to non-hypertensives.[17] Dussol found that HTN was present in 80% of type 2 diabetes patients.[19]

We noticed a lower prevalence of HTN in participants who reported tobacco smoking. Nebie *et al.* reported a prevalence of 23% of HTN in smokers.[20] The association between tobacco usage and HTN is still controversial and a possible confounding effect of both alcohol usage and overweight is being assumed.[21] The association of HTN with other cardiovascular risk factors contributes to increase the global cardiovascular risk of patients.

The results showed a higher prevalence of hypertension with worsening creatinine clearance rates. This was probably a consequence of hypertension, as shown by the decrease in creatinine clearance rate with the duration of hypertension.

Conclusion

This population-based survey is the first performed in Senegal. It was intended to serve as a baseline situation for other surveys locally or at a national level. We found a high prevalence of hypertension associated with other cardiovascular risk factors such as diabetes, obesity, inactivity and dyslipidaemia. The majority of participants were not aware of their condition.

Nationwide surveys are needed to better assess the burden of cardiovascular disease in this population. This will help authorities to formulate and implement adequate strategies to control hypertension and the emerging epidemic of non-communicable diseases.

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Pre-treatment before coronary artery bypass surgery improves post-operative outcomes in moderate chronic obstructive pulmonary disease patients

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Abstract

Introduction: **Chronic obstructive pulmonary disease (COPD) has traditionally been recognised as a predictor of poorer early outcomes in patients undergoing coronary artery bypass grafting (CABG). The aim of this study was to analyse the impact of different COPD stages, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric criteria, on the early surgical outcomes in patients undergoing primary isolated non-emergency CABG**

Methods: **Between January 2008 and April 2012, 1 737 consecutive patients underwent isolated CABG in the Department of Cardiovascular Surgery of Gulhane Military Academy of Medicine; 127 patients with the diagnosis of moderate-risk COPD were operated on. Only 104 patients with available pulmonary function tests and no missing data were included in the study. Two different treatment protocols had been used before and after 2010. Before 2010, no treatment was applied to patients with moderate COPD before the CABG procedure. After 2010, a pre-treatment protocol was initiated. Patients who had undergone surgery between 2008 and 2010 were placed in group 1 (no pre-treatment, n = 51) and patients who had undergone surgery between 2010 and 2012 comprised group 2 (pre-treatment group, n = 53). These two groups were compared according to the post-operative morbidity and mortality rates retrospectively, from medical reports.**

Results: **The mean ages of the patients in both groups were 62.1 ± 7.6 and 64.5 ± 6.4 years, respectively. Thirty-nine of the patients in group 1 and 38 in group 2 were male. There were similar numbers of risk factors such as diabetes, hypertension, renal disease (two patients in each group), previous stroke and myocardial infarction in both groups. The mean ejection fractions of the patients were 53.3 ± 11.5% and 50.2 ± 10.8%, respectively. Mean EuroSCOREs of the patients were 5.5 ± 2.3 and 5.9 ± 2.5, respectively in the groups. The average numbers of the grafts were 3.1 ± 1.0 and 2.9 ± 0.9. Mean extubation times were 8.52 ± 1.3 hours in group 1 and 6.34 ± 1.0 hours in group 2. The numbers of patients who needed pharmacological inotropic support were 12 in group 1 and five in group 2. Duration of hospital stay of the patients was shorter in group 2. While there were 14 patients with post-operative atrial fibrillation (PAF) in group 1, the number of patients with PAF in group 2 was five. Whereas there were seven patients who had pleural effusions requiring drainage in group 1, there were only two in group 2. There were three mortalities in group 1, and one in group 2. There were no sternal infections and sternal dehiscences in either group.**

Conclusion: **Pre-treatment in moderate-risk COPD patients improved post-operative outcomes while decreasing adverse events and complications. Therefore for patients undergoing elective CABG, we recommend the use of medical treatment.**

Keywords: cardiac surgery, complication, EuroSCORE, morbidity, risk factors

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Chronic obstructive pulmonary disease (COPD) is one of the leading causes of chronic morbidity and death in the world and it has traditionally been recognised as a predictor of poorer early outcomes in patients undergoing coronary artery bypass grafting (CABG).[1,2] The EuroSCORE system also includes chronic lung disease as an independent predictor of operative mortality, although with a generic definition not necessarily reflecting disease severity.[3] By contrast, some recent studies deny the association between COPD and increased early morbidity and mortality risk after CABG. Given the heterogeneity of clinical and/or spirometric variables used to define COPD by these different authors,[2] and the continuous emphasis recent guidelines place on the importance of spirometry as the gold standard for the diagnosis and staging of severity in COPD patients (GOLD guidelines update available at http://www.goldcopd.org),[4] further investigation on this topic was deemed necessary.

Post-operative complications such as respiratory failure, prolonged intubation time, intensive care unit (ICU) and hospital stay, sternal dehiscence and post-operative rhythm disturbances (mainly atrial fibrillation) are common in COPD patients.[1] Standard median sternotomy and cardiopulmonary bypass (CPB) have negative effects on pulmonary function. Pleurotomy during the harvesting of the left internal thoracic artery (LITA) and pain (due to chest tubes and incisions) may also negatively affect the patient's lung capacity. Patients with moderate COPD already have limited lung capacity and these patients may be severely affected by the effects of both CPB and the surgical trauma.[5]

The purpose of this study was to analyse the impact of pre-treatment in moderate COPD patients, as defined by the

Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric criteria,[4] on early surgical outcomes in patients undergoing primary isolated non-emergency CABG.

Methods

Between January 2008 and April 2012, 1 737 consecutive patients underwent an isolated CABG operation in the Department of Cardiovascular Surgery of Gulhane Military Academy of Medicine. Patients were identified from a prospectively maintained surgical database, and medical charts were reviewed retrospectively. Of these 1 737 patients, 127 with a diagnosis of moderate-risk COPD were operated on. Of these 127 patients, only 104 with available pulmonary function tests and no missing data were included in the study. Exclusion criteria were significant valve disease, emergency operation, and approaches other than median sternotomy, and surgical procedures other than CABG.

According to the practice of the Department of Pulmonary Diseases, two different treatment protocols were used before and after 2010. Before 2010, no treatment was applied to patients with moderate COPD before the CABG procedure. After 2010, a pre-treatment protocol was initiated (inhaled bronchodilator and steroid treatment for 10 days before the day of surgery). Patients who had undergone surgery between 2008 and 2010 comprised group 1 (no pre-treatment) and patients who had undergone surgery between 2010 and 2012 made up group 2 (pre-treatment group). These two groups were compared according to the post-operative morbidity and mortality rates retrospectively, from medical reports.

According to the GOLD COPD 2011 guideline, COPD was defined as a common, preventable and treatable disease, characterised by persistent airflow limitations, which are usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles and gases. Clinical diagnosis of COPD should be considered in a patient who has dyspnoea, chronic cough, or sputum production and/or a history of exposure to risk factors for the disease.

Spirometry is required to make the diagnosis in this clinical context; the presence of a post-bronchodilator and FEV_1/FVC < 0.70 (forced expiratory volume/forced vital capacity) confirms persistent airflow limitations and therefore COPD. According to the GOLD COPD 2012 guideline, the severity of airflow limitations in COPD is classified into four levels. In this classification, moderate COPD patients are defined as 50% ≤ FEV_1 < 80%, predicted in patients with FEV_1/FVC < 0.70.

A pulmonary function test (spirometry) was performed according to the previously described guidelines. FEV_1, FVC and FEV_1/FVC were expressed according to the reference values published by the European Respiratory Society in 1993. All surgical records were reviewed to determine the surgical procedure performed, cardioplegic technique, cross-clamp time, cardiopulmonary bypass times, number of grafts, left internal thoracic artery (LITA) usage, and number of blood products used.

An isolated CABG procedure was performed in all patients. Standard anaesthesia and surgical technique, extracorporeal circulation and myocardial protection methods were used. A median sternotomy approach was done in all patients. CPB was installed through the ascending aorta and right atrial cannulation and it was performed with roller pumps and membrane oxygenation. Myocardial protection was intermittent cold blood cardioplegia. All patients received antegrade cardioplegia and 'hot-shot' (reperfusion with warm cardioplegia). The lowest core temperature was between 28 and 32°C, depending on the surgeon's preference.

The patients were transferred to the ICU just after the operation and they received ventilator assistance and monitoring. Extubation was undertaken when the patient's criteria were stable, and time to extubation was also recorded.

The primary outcome was post-operative mortality in hospital and at 30 days. Secondary outcomes included the length of hospital stay, length of stay in ICU, time to extubation, re-intubations, pulmonary infections, pneumothorax, pleural effusions, atrial fibrillation, other arrhythmias, mediastinitis and sternal dehiscence, need for inotropic support, and low-cardiac output syndrome (LCOS).

Pulmonary infections included pneumonia and bronchitis. Pneumonia was defined by radiological evidence of new infiltration, consolidation or cavity, and antibiotic usage in the presence of one of the three following criteria: purulent sputum, positive blood culture or positive bronchial secretion culture. Bronchitis was defined by the presence of purulent sputum production and antibiotic use. Pleural effusion was included in the analysis only if it required drainage during hospitalisation. Arrhythmias other than atrial fibrillation included supraventricular arrhythmias, atrio-ventricular block requiring pacemaker, ventricular tachycardia, ventricular fibrillation and asystole. LCOS was considered when postoperative inotropic support was used for more than 24 hours.

Statistical analysis

Statistical analysis was performed with SPSS 15.0 for Windows. Continuous data were presented as mean ± SD. Nominal data were presented as frequencies and percentages. Differences were analysed with Levene's test, Fischer's exact test, the Mann-Whitney *U*-test and chi-square test.

Results

The mean ages of the patients in both groups were 62.1 ± 7.6 and 64.5 ± 6.4 years, respectively. Thirty-nine of the patients in group 1 and 38 in group 2 were male. Mean FEV_1 values of the patients in both groups were 46.1 ± 2.3% and 48.2 ± 2.1%, respectively. Mean ejection fractions of the patients were 53.3 ± 11.5% and 50.2 ± 10.8%, respectively. Mean EuroSCOREs of the patients were 5.5 ± 2.3 and 5.9 ± 2.5, respectively in both groups. There were similar risk factors in both groups, such as diabetes, hypertension, renal disease (two patients in each group), previous stroke and myocardial infarction. Demographic details of the patients are summarised in Table 1.

With regard to the primary outcome, there were three mortalities in group 1, and one in group 2. The causes of death included cardiogenic shock (n = 2), sepsis and multi-organ failure (n = 1), and cerebrovascular accident (n = 1).

There was no statistically significant difference between the groups with regard to CPB time, cross-clamp time and average graft numbers. However, when we looked at the mean extubation

times, there was a statistically significant difference between the groups. Extubation times were shorter in group 2 (group 1: 8.52 ± 1.3 and group 2: 6.34 ± 1.0 hours; $p = 0.032$).

While there were seven patients who had pleural effusions requiring drainage in group 1, there were only two patients with pleural effusions requiring drainage in group 2 ($p = 0.044$). Whereas there were 14 patients with post-operative atrial fibrillation (PAF) in group 1, the number of patients with PAF was five in group 2 ($p = 0.031$). All PAF patients excluding two were converted medically (amiodarone) to sinus rhythm in group 1. The remaining two were converted to sinus rhythm by D/C cardioversion. In group 2 all five patients with PAF were converted to sinus rhythm medically.

The number of patients who needed pharmacological inotropic support was 12 in group 1 and five in group 2. Pulmonary infections such as pneumonia were more frequent in group 1 compared to group 2. There were no sternal infections or sternal dehiscence in either group. The duration of ICU and hospital stay was shorter in group 2. Post-operative data of the patients are detailed in Table 2.

Discussion

CABG is a safe and effective surgical treatment that is performed successfully in a wide variety of patients.[1] Nowadays the profile of patients undergoing CABG is changing to a higher-risk profile; elderly patients with co-morbid medical problems. With improved experience, cardiac risk factors such as left main coronary artery disease and angina class have lost their predictive value for mortality in favour of extra-cardiac factors such as peripheral vasculopathy, chronic renal failure or COPD.[6,7]

The impact of COPD in patients undergoing open-heart surgery is potentially problematic because of the additional influence of CPB and median sternotomy.[8] It is well known that CPB interferes with pulmonary function. CPB can also induce adverse effects on alveolar stability by activating the complement system, sequestration of neutrophils in the pulmonary vascular bed, releasing oxygen-derived free radicals and changing the composition of alveolar surfactant.[8] Atelectasis is one of the most important problems after CPB, especially in the early post-operative period.

Median sternotomy also has a negative influence on pulmonary function. Structural changes in the chest wall after sternotomy are the cause of restrictive pulmonary dysfunction, which can be prolonged for weeks after the operation. Lung injury becomes more prominent after surgery in COPD patients. Therefore COPD has been established as an important risk factor for mortality in patients undergoing CABG.[7]

Depending on the severity of the pulmonary dysfunction, the morbidity and mortality of the procedure can be very high and sometimes almost prohibitive. Therefore a correct diagnosis and defining its severity is mandatory because it could allow better planning strategies.[9] In high-risk patients, it is imperative to institute vigorous pre-operative measures to improve the respiratory status before the surgical procedure. The degree of severity of these risk factors has an important prognostic relevance and not the risk factor itself. Mild COPD is well tolerated by CABG patients in comparison with moderate or severe COPD. As indicated by Fuster *et al*.,[7] FEV_1 must be the reference variable when a patient with COPD is considered for CABG, as is the creatinine level for chronic renal failure patients.[7]

Morbidity due to COPD usually increases with age and is higher in males than females.[10] In their study, Fuster *et al*.[7] reported that the mortality rate was 13% in patients over 75 years, while it was 7% in patients under 75 years. In our study, the patient population was on average 65 years, which was younger than Fuster's patient population, and we had three mortalities in group 1 and one in group 2.

Adverse respiratory system events such as respiratory failure and pneumonia have traditionally been the leading cause of post-operative complications.[11] COPD patients particularly are

TABLE 1. PATIENT CHARACTERISTICS

Variable	*Group 1 (*n = *53)*	*Group 2 (*n = *51)*	p-*value*
Age (years)	62.1 ± 7.6	64.5 ± 6.4	0.856
BMI	27.7 ± 3.1	28.2 ± 2.7	0.943
Gender			
Male	39	38	0.842
Female	14	13	0.911
Hypertension	32		0.932
Diabetes	17	35	0.731
Renal disease	2	20	1
NYHA class	1.9 ± 0.7	2	0.911
Mean FEV_1 (%)	46.1 ± 2.3	2,0 ± 0.8	0.823
EF (%)	53.3 ± 11.5	48.2 ± 2.1	0.678
Previous MI	23	50.2 ± 10.8	0.956
Previous stroke	3	24	0.745
CRF	2	2	1
EuroSCORE	5.5 ± 2.3	2	0.821

BMI: body mass index, NYHA: New York Heart Association, FEV: forced expiratory volume, EF: ejection fraction, MI: myocardial infarction, CRF: chronic renal failure.

TABLE 2. POST-OPERATIVE VARIABLES OF THE PATIENTS

Variable	*Group 1 (*n = *53)*	*Group 2 (*n = *51)*	p-*value*
Cross-clamp time (min)	67.2 ± 16.7	65.4 ± 19.2	0.453
CPB time (min)	140.5 ± 43.6	135.3 ± 50.4	0.654
Average number of grafts	3.1 ± 1.0	2.9 ± 0.9	0.744
Extubation time (h)	8.52 ± 1.3	6.34 ± 1.0	0.032
Re-intubation	1	–	0.5
Sternal dehiscence	–	–	–
Wound infections	1	–	0.5
Pleural effusions	7	2	0.044
Pneumonia	4	1	0.171
Mediastinitis	–	–	–
Atrial fibrillation	14	5	0.031
Other rhythm disturbances	–	–	–
Inotropic support	12	5	0.029
IABP support	3	2	0.742
LCOS	–	–	–
Length of ICU stay (days)	2.4 ± 1.2	1.4 ± 1.1	0.039
Length of hospital stay (days)	12.95 ± 2.4	8.29 ± 1.7	0.028
30-day mortality	3	1	0.302

CPB: cardiopuolmonary bypass, IABP: intra-aortic balloon pump, LCOS: low-cardiac output syndrome, ICU: intensive care unit.

at an increased risk for lower respiratory tract infections because of the immune-suppressing effects of CPB, combined with the respiratory flora of these patients.

As demonstrated by Gaynes *et al*.,[12] development of pneumonia following CABG in COPD patients was associated with a 27% mortality rate. In the study by Fuster *et al*.,[7] 18% of their moderate-to-severe COPD patients had post-operative pneumonia, with a mortality rate of 56%. In another study, Manganas *et al*.[13] reported more frequent pneumonia in COPD patients than in the control group (eight in the mild-to-moderate COPD group and two in the severe COPD group). In our study we had four pneumonia cases in group 1 and one in group 2.

Moreover, prolonged ventilation is known to result in increased ICU stay. Although in their study, Manganas *et al*.[13] found no difference between their study groups for prolonged mechanical ventilation and length of ICU stay, in our study, mean mechanical ventilation times and length of ICU stay of patients in group 1 were significantly longer than in patients in group 2. Similar to our findings, in Fuster's study,[7] incidence of prolonged ventilation and re-intubation was higher in moderate-to-severe COPD patients.

In a study by Bingol *et al*.,[1] the effect of prophylactic oral prednisolone in COPD patients was assessed. As a result they demonstrated that prophylactic treatment with prednisolone decreased both mechanical ventilation time and length of stay in ICU. These results were similar to our findings. From this point of view, it can be extrapolated that pre-treatment before surgery improves post-operative pulmonary function and shortens ICU stay.

Supraventricular tachyarrhythmias are common after CABG in COPD patients. In their study, Manganas reported 30% atrial fibrillation in the mild-to-moderate COPD group and 45% in the severe COPD group.[13] In Fuster's study,[7] the incidence of atrial fibrillation was lower than in the study by Manganas. The rate was 7.6% in the moderate group and 11.4% in the severe COPD group. In our study, there were 14 (26%) patients with atrial fibrillation in group 1 and five (9%) in group 2. For group 1, our results were similar to Manganas's study. From this, it can be concluded that the rate of atrial fibrillation was significantly lower in the pre-treatment group.

Optimisation of management in the pre-, peri- and post-operative periods may be the key to reducing the negative outcomes in this high-risk group.[14] It is important to improve the respiratory status of these patients by means of adjustment of their bronchodilator therapy and strict control by a physiotherapist. The correct timing of surgery is also mandatory in order to avoid the respiratory decompensation phases.[7] In the present study, we found that pre-treatment before surgery in moderate COPD patients improved early post-operative outcomes and decreased complications following CABG.

Conclusion

Pre-treatment in moderate-risk COPD patients improved post-operative outcomes while decreasing the adverse events and complications. We believe that in order to improve post-operative outcomes, a holistic approach must be applied for these patients. Not only bronchodilator treatment but also appropriate antibiotic treatment, besides physical exercise under strict control and perfect timing are key factors for the best results following CABG.

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Letter to the Editor

Isolated left ventricular non-compaction in Africa: elucidating myths

Dear Sir

We read with great interest the article by Falase *et al*. in the November 2012 issue of this journal.[1] They stated that there are no documented cases of left ventricular non-compaction in Africa. Furthermore, they propose that this is due to a lack of awareness of this condition among African cardiologists. The purpose of this letter is to highlight that this statement is not entirely accurate.

Isolated left ventricular non-compaction has been the subject of several case reports[2,3] occurring in individuals of sub-Saharan origin, as well as two large studies[4,6] (Table 1). The first large study that documented this condition included 54 individuals, all of African origin with no evidence of any congenital or acquired heart conditions associated with the phenotype of left ventricular non-compaction.[4]

This study showed that using comprehensive echocardiographic criteria could distinguish between normal individuals and those with left ventricular non-compaction. Furthermore, the burden of right ventricular non-compaction and papillary muscle abnormality in this condition was highlighted for the first time, which corresponds to findings from the largest pathology study conducted thus far.[5] We also recently described the myocardial mechanics of a cohort of subjects who fulfilled the echocardiographic criteria for isolated left ventricular non-compaction, with rigid body rotation occurring in 53% of subjects.[6]

It is important to note that currently, the only dedicated left ventricular non-compaction clinic in the southern hemisphere is based at the Chris Hani Baragwanath Hospital, where patients have now been followed up for up to 40 months. This centre has dealt with both national and international referrals, and offers echocardiographic techniques and CMR to aid diagnosis. In addition to standard medical therapy, patients with isolated left ventricular non-compaction have been treated with biventricular pacing and internal cardiac defibrillators in cases of refractory heart failure.

Isolated left ventricular myocardium is a condition encountered in clinical practice in Africa and needs to be identified and distinguished from acquired causes of left ventricular non-compaction. Long-term outcome and follow up have not been documented among patients of African origin and is the subject of future research initiatives.

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TABLE 1. ISOLATED LEFT VENTRICULAR NON-COMPACTION IN INDIVIDUALS OF SUB-SAHARAN ORIGIN

Authors	*Year of publication*	*Type of report*	*Sample size*	*Age (years)*	*Imaging technique*
Paule P, Braem L, Mioulet D, Jop B, Théron A, Gil JM, Héno P, Fourcade L[7]	2007	Case report	3	Range: 23–45	Echo and MRI
Massoure PL, Lamblin G, Bertani A, Eve O, Kaiser E[8]	2011	Case report	1	74	Echo
Peters F, dos Santos C, Essop R[2]	2011	Case report	1		Echo: Jenni criteria
Peters F, Khandheria BK, dos Santos C, Matioda H, Mogogane MT, Essop MR[3]	2012	Case report	2	35	Echo: Jenni criteria
Peters F, Khandheria BK, dos Santos C, Matioda H, Maharaj N, Libhaber E, Mamdoo F, Essop M[4]	2012	Large prospective series	54	Mean: 45.4 ± 13.1	Comprehensive criteria: combination of Jenni and Stolberger
Peters F, Khandheria BK, Libhaber E, Maharaj N, dos Santos C, Matioda H, Essop MR[6]	2013	Large prospective series	60	Mean: 47.01 ± 12.8	Comprehensive criteria: combination of Jenni and Stollberger

Review Article

Can stem cells really regenerate the human heart? Use your noggin, dickkopf! Lessons from developmental biology

PAULA SOMMER

Abstract

The human heart is the first organ to develop and its development is fairly well characterised. In theory, the heart has the capacity to regenerate, as its cardiomyocytes may be capable of cell division and the adult heart contains a cardiac stem cell niche, presumably capable of differentiating into cardiomyocytes and other cardiac-associated cell types. However, as with most other organs, these mechanisms are not activated upon serious injury. Several experimental options to induce regeneration of the damaged heart tissue are available: activate the endogenous cardiomyocytes to divide, coax the endogenous population of stem cells to divide and differentiate, or add exogenous cell-based therapy to replace the lost cardiac tissue. This review is a summary of the recent research into all these avenues, discussing the reasons for the limited successes of clinical trials using stem cells after cardiac injury and explaining new advances in basic science. It concludes with a reiteration that chances of successful regeneration would be improved by understanding and implementing the basics of heart development and stem cell biology.

Keywords: heart development, stem cell clinical trials, iPS cells, ES cells, paracrine signalling

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Development of the heart

Human development begins with the fertilisation of an ovum by a sperm, initiating furious but intricately controlled cell division. At implantation, the embryo is known as a blastocyst, consisting of an outer trophoblast and an inner cell mass composed of embryonic stem (ES) cells. These ES cells divide, move, respond to cues from themselves and each other, and demonstrate pluripotency, the ability to develop into all the tissues and organs of the human body.

As the embryo develops into a foetus, the cells lose pluripotency and progress towards a more differentiated state, contributing to the formation of organs. Their potency therefore becomes more and more restricted. Every organ and tissue in the adult body retains a niche of stem cells whose potency is generally specific to the cells of the resident tissue.

The heart is the first organ to form in the developing embryo. The vertebrate heart develops from two regions of splanchnic mesoderm, one on each side of the developing embryo, that interact with the directly adjacent tissue, the anterior endoderm. The presence of the anterior endoderm is essential for heart development, and the interaction between these two tissues results in the specification of cells destined to form the heart – the cardiogenic mesoderm.[1] The presence of certain cardiac-restricted transcription factors such as *Gata4*[2] and *Nkx2-5*[3] are essential for restricting the mesoderm to a cardiac fate.

The anterior endoderm secretes factors such as bone morphogenetic proteins (BMPs) and fibroblast growth factors (FGFs). The *Bmp2* gene particularly plays a role as, in mice in which the *Bmp2* gene has been knocked out (*Bmp2*$^{-/-}$ mice), the heart either does not develop or develops poorly.[4] This range of different phenotypes suggests a degree of genetic redundancy, where other BMPs compensate for the lack of *Bmp2*. Such effects are also noted for the different FGFs.

Along with the positive signals initiating heart development, inhibitory signals prevent the heart from forming where it shouldn't. The notochord, which serves to define the central axis of the embryo, secretes the BMP inhibitors noggin and chordin, preventing the heart from forming in the centre of the embryo. The anterior endoderm secretes Wnt inhibitors such as cerebrus, dickkopf and crescent, which prevent Wnts from binding to their receptors. Therefore cardiac precursor cells are specified in the places where BMPs (from the lateral mesoderm and endoderm) and Wnt antagonists (from the anterior endoderm) coincide.[5]

This simplified description of heart development serves to show that there is no straightforward recipe for the development of the human heart. There is, however, information that can be exploited.

Key message: Heart development is a complex process promoted by positive signals such as BMPs and shaped by negative signals such as the Wnt inhibitors, cerebrus and dickkopf, and the BMP inhibitors, noggin and chordin.

Can the human heart be induced to regenerate after injury?

An estimated 17 million people worldwide die annually from cardiovascular disease, particularly heart attacks and strokes (http://www.who.int/cardiovascular_diseases/resources/atlas/

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en/). Cardiovascular disease is also prevalent in South Africa, resulting in 195 deaths per day between 1997 and 2004 (http://www.mrc.ac.za/chronic/heartandstroke.pdf).

The major cause of heart failure is the death of cardiomyocytes, where a typical large myocardial infarct (MI) kills around one billion myocytes (one-quarter of the heart).[6] The current treatments do not address the problem of the reduced pool of cardiomyocytes but rather involve transplantation or insertion of mechanical ventricular assist devices.

For many years, prevailing dogma insisted that the heart was a static post-mitotic organ incapable of regeneration. While heart tissue has shown a capacity to regenerate, there is intense controversy over whether cardiomyocyte division plays a role in regeneration. Some *in vivo* studies have shown evidence of possible cardiomyoctye division, although they fail to agree on the rate of cardiomyocyte turnover,[7,8] and have been heavily criticised for their methodology.[9] Regardless, it is evident that their possible ability to divide does not extend to repairing extensively damaged heart tissue.

The heart has also been shown to harbour a compartment of multi-potent cardiac stem cells and other progenitor cells that can differentiate into myocytes and coronary vessels. Again, there has been much controversy surrounding this discovery. Some believe that new myocytes may arise from the de-differentiation of mature myocytes back to their immature state, allowing them to acquire an immature phenotype and therefore to divide.[10]

There are those that query whether the identified cardiac stem cell population is fully distinct from haematopoetic stem cells (HSCs) in the bone marrow, as these cells are able to enter the circulation, home to organs and trans-differentiate, acquiring a myocyte lineage.[11] This was initially a surprising finding as only embryonic stem cells are pluripotent, and as they contribute to the development of tissues, their potency becomes more and more restricted to cells of that tissue.

It is thought that commitment to a developmental fate is irreversible but plasticity has been shown, particularly with HSCs. This line of thought has been heavily criticised, with studies showing that HSCs cannot trans-differentiate into cardiomyocytes after MI.[12,13]

The existence of a c-kit$^+$ population of cardiac stem cells able to self-renew and to differentiate into cardiomyocytes, smooth muscle and endothelial cells has been demonstrated.[14] Detractors argue against the existence of these cells, reasoning that spontaneous repair after injury does not occur. However, stem cell niches have been described in many organs and while these cells have been shown to play a role in regulating tissue homeostasis, many do not effectively respond to aging or injury, possibly because the adult environment is not permissible.

Key message: Several experimental options to induce regeneration of damaged heart tissue require investigation: activation of the endogenous populations of cardiomyocytes and/or stem cells, or the addition of exogenous cell-based therapy to replace lost cardiac tissue.

Exogenous cell-based therapy: the different types of stem cells used in clinical trials for heart regeneration after injury

There are currently 30 to 40 registered clinical trials using different types of stem cells to treat various types of cardiovascular disease (http://www.clinicaltrials.gov/; www.clinicaltrialsregister.eu[15]). The overwhelming majority of the registered trials, completed, on-going or not yet recruiting, involve the use of stem cells derived from the bone marrow. The bone marrow is an attractive source of stem cells as the cells can be obtained relatively easily. The bone marrow contains a hetergoneous population of stem cells of various lineages (including the blood mononuclear cells, B-cells, T-cells and monocytes, as well as rare progenitor cells such as haematopoietic stem cells, mesenchymal stem cells, endothelial progenitor cells, CD_{34}^+ and CD_{133}^+ cells).[16]

The bone marrow stem cell fraction can either be administered whole or distinct bone marrow cell populations can be isolated on the basis of specific cellular markers. Approximately half the registered trials use whole bone marrow fractions while the others use specific cells purified, using specific markers, from the bone marrow fraction. These include bone marrow mononuclear cells, bone marrow-derived mesenchymal stem cells, endothelial cells, CD_{34}^+ and CD_{133}^+ cells.

Treatment with G-CSF (granulocyte colony-stimulating factor) stimulates the movement of bone marrow stem cells into the bloodstream and has been used in trials of patients suffering from cardiovascular disease, either as the sole treatment to incite movement of bone marrow stem cells into the bloodstream or in conjunction with administration of stem cells. Trials have been performed with both autologous and allogeneic bone marrow stem cells. The majority of trials using bone marrow stem cells use autologous bone marrow stem cells, whole or purified.

Although cardiac stem cells are more difficult to isolate, as they can only be harvested from endomyocardial biopsies and require careful growth conditions and identification using markers such as c-kit, Sca-1 and Isl-1, trials have also been performed with autologous cardiac stem cells. One of these trials is slightly more complex and involves the addition of cardiac stem cells along with a bFGF gel mat during coronary artery bypass surgery for local release of bFGF.[17] As there are those who are concerned about the 'stemness' of cardiac stem cells (the ability of these cells to form cardiac tissue), there is a trial using autologous cardiospheres. When cardiac stem cells derived from biopsies are allowed to grow *in vitro*, the cells form spheres, hence cardiospheres, and are presumably more committed to a cardiac stem cell fate.

Key message: Both bone marrow and cardiac-derived stem cells have been used or are currently being used in clinical trials to determine whether these cells could contribute to cardiac repair.

Does exogenous administration of autologous or allogeneic stem cells aid in cardiac repair?

Results from randomised trials using bone marrow mononuclear cells demonstrated modest cell therapy-mediated improvements in ventricular function.[9] In one of the largest studies to date, 204 randomised patients diagnosed with acute MI received intracoronary delivery of bone marrow cells or vehicle control. After one year these patients showed significant improvements in cardiac function.[18] A two-year follow up revealed that these positive effects were preserved.[19]

The authors showed experimentally that less than 20% of the administered stem cells were retained in the heart,[20] which indicates that some cells do home in on the target tissue, but it also shows that only a few cells are needed to exert positive

effects. These results are in contrast to those obtained by a similarly constructed study where patients suffering from acute ST-segment elevation MI were administered bone marrow-derived stem cells. While initial results were promising,[21] the 18-month and five-year follow ups have shown that, while the treatment had an overall positive effect, this was attributed to the early improvement, with little sustained effect seen.[22]

The general consensus is that bone marrow stem cell treatment moderately improves heart function, does not decrease mortality or morbidity significantly in long-term follow up, and has, as yet, not been associated with any significant safety concerns.[23] How these cells act to repair the damaged tissue is not known. Some believe that the bone marrow cells trans-differentiate into cardiomyocytes.[10] However, it is generally believed that these cells secrete paracrine factors, creating a permissible environment, which stimulates the endogenous cardiomyocyte progenitor cells or adult cardiomyocytes to divide. While this is entirely probable, there is little evidence for this.

Similarly, trials using selected cell populations such as endothelial progenitor cells (which promote angiogenesis and possibly secrete paracrine factors that may promote cardiomyocyte division) or mesenchymal stem cells (which can differentiate into cardiomyocytes although the rate of differentiation is low) isolated from bone marrow have shown similar results to the whole bone marrow fraction studies described.[9]

One of the first trials, the Stem Cell Infusion in Patients with Ischemic cardiOmyopathy or SCIPIO trial, using purified cardiac stem cells, has recently produced interim results. In this study, autologous c-kit$^+$ cells were isolated and grown from tissue harvested during coronary artery bypass surgery, and administered to the patient at a later stage by intracoronary infusion. Cardiac magnetic resonance showed that, not only is the procedure feasible, but also that administration of the cells produced a striking improvement in both global and regional left ventricular function, a reduction in infarct size, and an increase in viable tissue, which persisted at least one year after administration, consistent with cardiac regeneration.[24,25]

Initial results from the CADUCEUS (CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction) randomised, controlled trial have also been released. Here, after myocardial infarction, autologous cardiac stem cells were isolated from endomyocardial biopsy specimens and allowed to grow *in vitro* to form cardiospheres. These were then administered via intracoronary delivery. Initial results indicate that the process is safe and viable, and showed a decrease in scar tissue mass after MI, and regeneration of viable myocardium.[26]

It is possible that the positive results of the cardiac stem cells and cardiosphere trials are not due to direct stem cell action,[27] as the cardiac 'stemness' of cardiac stem cells and cardiospheres has been questioned. Using an elegant labelling technique where transgenic mice were generated with enhanced green fluorescent protein under the control of the c-kit gene promoter, a report showed that, while c-kit marks cardiac progenitor cells during development, in the adult, it is not a marker for cells capable of cardiomyogenesis. This study shows that, at least in this experimental model, cardiac c-kit$^+$ cells[28] and cardiospehere-derived cells lack cardiomyogenic potential.[29]

All of these described trials were designed with the intent that the stem cells, whether bone marrow or cardiac derived, engraft into the diseased tissue and differentiate into functional cardiomyocytes. However, the results suggest that it is not that simple and that the modest improvements seen are probably due to the exogenous cells creating a permissible environment (by secreting factors and appropriate signals) that induces the endogenous cardiomyocytes or cardiac stem cells to proliferate. It is therefore suggested that basic knowledge of stem cell and developmental biology be exploited to further increase the positive effects seen thus far.[30]

Key message: Bone marrow or cardiac-derived stem cells do contribute to cardiac repair or survival, however, it seems that these cells do not contribute directly. Their action appears to be effected by paracrine secretions, which create a permissible environment for the endogenous repair mechanisms.

Exploitation of developmental and stem cell biology knowledge

The clinical trials described so far have had only marginal, if any, success. This may be due to the use of adult stem cells that lack the necessary plasticity to differentiate into cardiomyocytes. It may be that more highly plastic cells are needed to recapitulate cardiomyogenesis. In theory, this requirement should be satisfied by the use of cardiac stem cells, cells that should be able to differentiate into cardiomyocytes. However, it appears that they may not persist into adulthood or may express different markers in the adult. Their use is also complicated by the fact that autologous cardiac stem cells are harvested after damage to the heart and, generally, from older patients.

The most plastic or potent cells are ES cells. ES cells were first isolated from a human embryo in 1998 and since then, several ES cell lines have been created, which perpetuate in culture. These cells cannot simply be administered to patients, as their intrinsic potency and ability to divide causes teratomas, even several years after therapeutic delivery.

These issues can be overcome by directing human ES cells along a pathway of differentiation towards a cardiomyocyte lineage. Various recipes involving sequential exposure to BMP2, FGF and Wnt, and BMP inhibitors as in normal heart development have been shown to generate cells with the potential to form cardiomyocytes, smooth muscle and endothelial cells. When transplanted into primates, these cells did not form teratomas but contributed to the repair of scar tissue. The rationale behind this basic work is to generate a pool of pure ES-derived cardiomyocytes, which could be used for 'off-the-shelf' therapy.[31] This is a clever but very expensive approach that is still muddied by the initial use of ethically controversial ES cells.

Induced pluripotent stem (iPS) cells are adult, somatic cells which have been re-programmed by the addition of three or four embryonic transcription factors to become pluripotent. These cells overcome the ethical concerns created by embryonic stem cells and also graft rejection, as they can be engineered from a patient's own stromal cells for autologous transplantation.

Mouse embryonic fibroblasts were induced to become pluripotent by forced expression of the pluripotency markers, OCT3/4, SOX2, KLF4 and c-MYC. These iPS cells were administered to athymic nude mice after the induction of myocardial ischaemia by left coronary artery ligation. These cells did not form tumours and successfully integrated into the allogeneic host heart parenchyma, contributing to tissue reconstruction with synchronised cardiovasculogenesis.[32]

These initial studies in animal models are promising, however re-programming involves using viruses to introduce the pluripotency factors into the cells, creating concerns. The elimination of the need for viruses to re-programme the cells would make iPS cells a very attractive option for the generation of cardiomyocytes.

Another option is simply to skip the induction of pluripotency and directly re-programme somatic cells into functional cardiomyocytes. Research has shown that cardiomyocyte-like cells can be derived from directly re-programming post-natal dermal or cardiac fibroblasts, using three developmental transcription factors: *Gata4, Mef2c* and *Tbx5*.[33] Indeed, these cells have been shown in mouse models of MI to contribute to decrease in infarct size. As with the iPS cells, however, the use of viruses to re-programme the cells still prevents translation into clinical trials.

While all of these options are possible if the procedures are made virus free, perhaps the simplest option would be to circumvent cell-based therapy. All the clinical trial evidence thus far points to the fact that the stem cells create a permissible environment via paracrine signalling that serves to amplify the endogenous regenerative response and/or stimulate cell cycle re-entry of endogenous cardiomyocytes. Adult stem cells, particularly mesenchymal stem cells, have been shown to secrete a wide variety of factors that promote protection of the myocardia, neovascularisation, cardiac remodelling, and improve contractility.[34] The use of these molecules alone as a treatment to stimulate endogenous cardiac repair is an exciting and promising avenue of research.

Key message: Cardiomyocytes can be synthetically created from ES, iPS or even by simple trans-differentiation of somatic cells using developmental cues. However, the creation of these cells involves the use of viruses, which pose a risk to patients. Paracrine factors are postulated to contribute to the positive results seen in clinical trials. Identification of the secreted molecules could pave the way for cell-free mechanisms of stimulating the endogenous repair mechanism.

Conclusions

There are numerous on-going or completed clinical trials to assess the abilities of bone marrow or cardiac-derived stem cells to regenerate cardiac tissue destroyed by cardiovascular disease. These trials have been shown to have limited success. It appears that, although the initial aims of these trials were that the exogenous stem cells would directly contribute to cardiac repair by integrating into the target tissue, proliferating and differentiating into cardiac-associated cell types, the positive action exerted by these cells may be indirect.

It is believed that stem cells secrete various growth factors, cytokines and signalling molecules that stimulate the endogenous stem cells or cardiomyocytes to proliferate. The inability of the exogenously administered stem cells to contribute directly may be due to their lack of potency. It is therefore thought that, to regenerate substantial cardiac tissue, either synthetically generated stem cells such as iPS or directly re-programmed somatic cells (generated without the use of viral vectors) are a more feasible, though expensive, option.

It is clear that understanding of the molecules that direct heart development and the environment in which the heart develops, and the use of this information in creating new treatments is essential. The development of a 'cell-free' treatment with the administration of molecules that either stimulate the endogenous cardiomyocytes, or stem cells to divide, or molecules that create a permissive environment to stimulate regeneration would be an ideal solution, eliminating the need for surgery.

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CARDIOVASCULAR CONGRESS DIARY 2013

DATE	PLACE	CONFERENCE	CONTACT DETAILS TO REGISTER
JULY 2013			
13–15 July	Asian Federation of Cardiology congress (AFCC)	Singapore	www.afcc2012.com
AUGUST 2013			
25–29 August	2012 ESC, European Society of Cardiology congress	Munich, Germany	www.escardio.org
SEPTEMBER 2013			
11–13 September	6th international symposium on hybrid approach to congenital heart disease 2012	Columbus, US	www.nationwidechildrens.org/ishac-home
OCTOBER 2013			
10–12 October	Federation of Infectious Disease Society in South Africa (FIDSSA)	Drakensberg, SA	www.fidssa.co.za
13–16 October	10th international congress on coronary and artery disease from prevention to intervention (ICCAD)	Florence, Italy	www.kenes.com/iccad
NOVEMBER 2013			
16–20 November	86th American Heart Association scientific sessions (AHA)	Dallas, Texas, USA	http://my.americanheart.org/
	Critical care refresher course 2013	SA	www.criticalcare.org.za
21–24 November	5th international conference of fixed combination in the treatment of hypertension, dyslipidaemia and diabetes mellitus	Bangkok, Thailand	www.fixedcombination.com/2013

Conference Report

4th All-African conference on heart disease, diabetes and stroke 11th Pan-African Society of Cardiology (PASCAR) conference

Cardiovascular disease is on the rise in Africa. Evidence indicates an increased prevalence of ischaemic heart disease, diabetes, stroke, cardiomyopathies, congenital heart disease, rheumatic heart disease and disease of the pericardium (HIV/AIDS). Highlights from the PASCAR meeting hosted in Dakar, Senegal, 16–20 May 2013, are reported below. The full set of abstracts can be viewed at http://www.cvja.co.za/onlinejournal/vol24/pascar_2013.

Hypertension

Hypertension is a silent killer, remaining undiagnosed in 30–90% of people in varying socio-economic circumstances. Hypertension is the most widespread cardiovascular disease, affecting over one billion people worldwide. In sub-Saharan Africa, hypertension is the third highest risk factor for myocardial infarction, after diabetes mellitus and smoking. Furthermore, 50% of stroke deaths are linked to hypertension.[1]

Guidelines for the diagnosis of hypertension in Africa should include repeated blood pressure measurements in the office, self-measurement (12 hourly over three days) and ambulatory blood pressure monitoring.[1,2] A comprehensive family and clinical history should be investigated and a physical examination performed. Routine laboratory investigations and instrumental tests should include:

- fasting plasma glucose
- serum total cholesterol, LDL cholesterol, HDL cholesterol
- fasting serum triglycerides
- serum potassium
- serum uric acid
- serum creatinine

'The growing epidemic of non-communicable disease is a crisis of our own creation, … through poor choices of lifestyle and urbanisation.'

Walinjom Muna, Cameroon

'It is staggering to consider the grave consequences of lack of action now.'

Samuel Omokhodion, Nigeria

- estimated creatinine clearance
- haemoglobin and haematocrit
- urinalysis
- electrocardiogram.

Lifestyle choices can assist in preventing the development of hypertension or help manage blood pressure levels. Systolic blood pressure reductions are associated with the cessation of smoking; a reduction of weight (5–10 mmHg/10 kg), salt intake (2–8 mmHg), saturated and total fat intake, as well as excessive alcohol intake (2–4 mmHg); and increased physical activity (4–9 mmHg) and intake of fruit and vegetables.

Pharmaceutical intervention is required should lifestyle alterations not deliver sufficient benefits in maintaining blood pressure targets. Monotherapy is effective in a limited number of patients only (those with mild blood pressure elevation and low-to-moderate total cardiovascular risk), and more than one drug is usually required to achieve blood pressure targets. A significant decrease in the incidence of stroke has been noted when comparing the use of combination therapy to monotherapy.

Of the drug combinations tested or widely used, a beta-blocker/diuretic combination favours the development of diabetes. Treatment needs to be individualised to the patient to ensure tolerance. If hypertension is not controlled at six months, pill-taking behaviour should be checked. If adherence is sound, a third hypertensive agent can be added. Ideally, fixed drug combinations are required to simplify treatment and improve compliance.[2]

1. Moustapha Sarr. Epidemiology and diagnosis of hypertension in 2013.
2. Daniel Lemogoum. Guidelines for the management of hypertension in Africa: is an update needed?

Diabetes and obesity

The extent of diabetes mellitus in Africa is not yet appreciated by communities and decision makers.[1] Sub-Saharan Africa currently has a diabetes disease burden of 15 million, and is expected to double over the next 20 years. Of this disease burden, it is estimated that 81% of individuals with diabetes remain undiagnosed; not surprisingly, this region has the highest global diabetes mortality rate.[2]

Many barriers hinder effective prevention and management of diabetes. HIV is associated with diabetes and the metabolic syndrome, as is rapid urbanisation. Stigma issues surrounding obesity are problematic, with female obesity still considered attractive in some communities. On the African continent obesity is more common in females than in males; however obesity is an independent risk factor for diabetes in both genders.[1,2]

The paradox of malnutrition and obesity, historically urban, is increasingly described in rural communities as money from the cities moves into rural areas for development.[1,2] Maternal under-nutrition influences risk of cardiometabolic disease, with evidence of foetal under-nutrition conferring a higher risk of hypertension in later life. Hypothalamic control of appetite is modulated by early-life nutrition.[3]

Poverty, lack of access to clinics and a dearth of specialists on the African continent further contribute to the burden of disease. Often, in Africa, cardiovascular complications are already present at the time of diagnosis of diabetes. These complications could be avoided with earlier diagnosis and management of diabetes.[1] Biochemical screening tests recommended for diagnosing diabetes in

'Seven of the 10 top determinants of mortality in the world relate to how we eat, drink and move.'

Elijah Ogola, Kenya

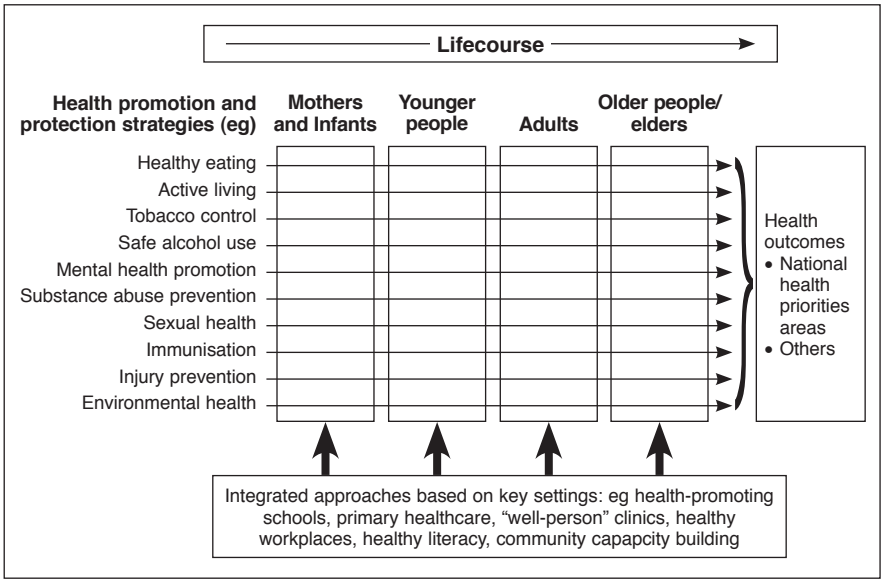

Fig. 1. Lifecourse perspective to chronic disease prevention.[2]

Africa are urine glucose, random blood glucose (dependant on the population-specific threshold), fasting plasma glucose, glycated haemoglobin, point-of-care capillary glucose, and 75- and 50-g oral glucose tolerance tests.

Lifestyle interventions remain the first consideration in the prevention and treatment of diabetes. Weight control, healthy eating and physical activity levels are strong determinants of disease progression. Drug affordability and availability are limiting factors in the medical management of diabetes. Monitoring and surveillance of complications and the treatment of complications and co-morbidities are essential to long-term diabetes care (Fig. 1).[2]

1. Said Norou Diop. Management of diabetes in Africa.
2. Andre Kengne. The appropriate public health response to the rise of obesity and diabetes in Africa.
3. Terence Forrester. The role of nutrition and early life influences on the pathogenesis and prevention of cardiometabolic diseases in Africans.

'A mountain of information emerging from our scientists on the African continent alerts us to a looming crisis. This is an important opportunity for scientists to report on disturbing trends with resgard to cardiovascular disorders in Africans.'

Samuel Omokhodion, Nigeria

Sickle cell disease: an update on the CADRE study

Sickle cell disease (SCD), also known as sickle haemoglobin and haemoglobin S, is an inheritable disorder resulting in sickling of red blood cells and chronic haemolysis. Haemoglobin has two subunit chains, alpha and beta, with the normal referred to as HbA. In SCD, the alpha-chain is normal but abnormal versions of beta-globin (e.g. HbS and HbC) are present. This results in a characteristic modification of the smooth doughnut shape of the red blood cell into a crescent shape. Cells then lack plasticity and can block small blood vessels, impairing blood flow. Shortened red blood cell survival also leads to subsequent anaemia.

Acute complications of SCD include vaso-occlusive pain (blood flow block, can occur anywhere but most commonly arms, legs, chest and spine) and chest syndrome (often occurs suddenly and can be life-threatening, resembles pneumonia, multiple episodes can cause permanent lung damage). Chronic vascular events include stroke, pulmonary hypertension, cardiac disease, nephropathy, retinopathy, leg ulcers and osteonecrosis.

Different types of SCD vary in sickle symptoms and disease severity, dependant on the inherited mutation.

- HbAS individuals carry the trait but usually display no signs and symptoms of disease.
- HbSS is the most common and severe form of SCD, with a variety of symptoms and complications.

'The omission of cardiovascular disease from the Millenium Development Goals has cost us years of action and millions of lives'.

Vash-Mungal Singh, South Africa

- HbSC presents mild to moderate complications.
- HbS-beta-thallasaemia comes in two forms: beta0 and beta+, with a broad range of symptoms and severity.
- Other forms.

Of children born with SCD, 90% are born in sub-Saharan Africa, implying a prevalence of greater than 25 million. Yet SCD data predominantly arises out of America and Europe, with very small studies of less than 250 patients.

CADRE is a multinational cohort for the study of SCD chronic vascular events in Africa. Study sites are in Senegal, Mali, Cote d'Ivoire, Cameroon and Gabon. Among the objectives of this first SCD multinational cohort is to build up the world's largest database of 4 500 SCD patients, to assess the prevalence of the main chronic micro- and macrovascular complications of SCD in Africa and to look for associations between these main complications, arterial stiffness and haematological parameters.

Clinical investigations of the study include socio-economic data, medical history and clinical examination. Functional investigations include echocardiography and pulse-wave velocity (PWV) measurements. Biological investigations include urine proteins and urine creatinine, blood creatinine, blood cell count and haemolysis markers.

Current CADRE results give evidence of two main SCD populations: SS, Sbeta0, SC and Sbeta+. In SCD patients carotid–femoral PWV = 7.8 (7.0–8.8) m/s versus 9.5 (8.4–10.7) in controls, even after adjustment for gender, age, blood pressure and BMI. The more severe SCD phenotypes (SS and Sbeta0) have lower PWV than others (SC and Sbeta+), even after adjustment for age, blood pressure and haemoglobin. Multivariate analysis indicates that PWV is independently correlated with age ($p < 0.001$), blood pressure ($p < 0.001$) and haemoglobin ($p = 0.01$). However, PWV is not correlated with LDH or bilirubin levels (haemolysis markers).

The CADRE study provides valuable data on the incidence of chronic vascular

events in African SCD patients. PWV is significantly lower in SCD patients than in controls, but may correlate positively with the vascular severity in each SCD population. The prognostic value of PWD and haemolysis markers will be further established during on-going follow-up studies.

B Ranque. The CADRE study (Coeur Arteres et Drepanocytose)

Quick facts: HIV-associated heart disease in Africans

Patrice Zabsonre, Burkina Faso

- Multifactorial pathogenesis of HIV-associated heart disease:
  - HIV infection of cardiomyocytes
  - Myocarditis
  - Other opportunistic infections
  - Mitochondrial toxicity
  - Cytokines
- Cardiac manifestations are predominantly HIV-related cardiomyopathy, pericardial disease and valve disease.
- Myocarditis virtually disappears after the introduction of highly active antiretroviral therapy (HAART).
- Incidence of chronic vascular disease increases with HAART-related improved survival.
- Despite a high prevalence of rheumatic heart disease, prevalence of endocarditis in HIV infection is unknown.

Quick facts: WHO–AFRO priorities for NCDs

Boureima Sambo, Congo

- Primary prevention: to promote interventions to reduce the main shared modifiable risk factors for NCDs
  - Tobacco and alcohol legislation
  - Improvement of unhealthy diets low in fruit and vegetable consumption
  - 'Active living adds years to life'
- NCD prevention and management at primary healthcare level:
  - Implement and monitor cost-effective early detection of NCDs
  - Establish standards of healthcare for common conditions
- Strategic plan for Africa to be adopted during the course of 2013 in line with the 2011 Brazzaville Declaration of NCD prevention and control

Quick facts: Rheumatic heart disease in Africa

Liesl Zulkhe (South Africa), Mark Engel (South Africa), Andre Samadoulougou (Burkina Faso), Serigne Ba (Senegal)

- Infection with β-haemolytic strain of Group A *Streptococcus* (GAS) leading to acute rheumatic fever. Recurrent rheumatic fever episodes lead to RHD.
  - Developing countries show a nine-fold burden of GAS disease compared to the developed world.
- Most frequent cause of heart failure in children and adults, with a 17.8% 180-day mortality.
- Females may be more likely to have RHD.
- Echo-based screening studies in South Africa indicate a higher prevalence than previously estimated.
- Earlier diagnosis requires:
  - Standardisation of echocardiographic screening, with simple criteria for non-expert staff
  - Evidence-based diagnostic criteria for RHD
  - Determining the significance of sub-clinical carditis
  - Determining the cost-effectiveness of echo screening, and making it practical and affordable.
- Pregnancy is contra-indicated in the presence of severe cyanosis, advanced heart failure and severe, irreversible pulmonary arterial hypertension.
- Favourable maternal outcomes are associated with prior cardiac events, prior surgical valve replacement and cardiac prosthetic valve.

G Hardy

Case Report

Acute myocardial infarction complicated by acute pulmonary oedema and cardiogenic collapse during dobutamine stress echocardiography

NOBILA VALENTIN YAMEOGO, ALASSANE MBAYE, LARISSA JUSTINE KAGAMBEGA, MOMAR DIOUM, DIOR DIAGNE-SOW, MOUSSA KANE, BOUNA DIACK, ABDOUL KANE

Abstract

Acute myocardial infarction is a rare complication of dobutamine stress echocardiography. We describe the case of a diabetic patient who presented with an anterior myocardial infarction complicated by an acute pulmonary oedema and cardiogenic collapse during dobutamine stress echocardiography, requiring five days' hospitalisation. Coronarography could not be performed because of inadequate medical facilities.

Keywords: Dobutamine stress echocardiography, acute myocardial infarction, complication

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DOI: 10.5830/CVJA-2013-021

Résumé

L'infarctus du myocarde est une complication rare de l'échocardiographie de stress à la dobutamine. Nous décrivons le cas d'un patient diabétique qui a présenté un infarctus du myocarde en antérieur compliqué d'un œdème aigu du poumon et d'un collapsus cardiogénique au décours d'une échocardiographie de stress à la dobutamine et ayant nécessité une hospitalisation de 5 jours en unité de soins intensifs cardiologiques. Une coronarographie n'a pu être réalisée à cause d'une insuffisance du plateau technique.

Mots clés: echocardiographie de stress à la dobutamine, infarctus du myocarde, complication

L'échocardiographie de stress (EDS) est un examen dit non invasif. Elle permet le diagnostic, le suivi et l'évaluation du pronostic d'une coronaropathie.[1-8] Elle est utilisée pour l'étude de la viabilité mais aussi la recherche et la quantification de l'ischémie myocardique.

Il existe deux modalités de réalisation à savoir l'effort ou la perfusion d'une drogue inotrope et chronotrope positive (dobutamine le plus souvent). L'étude de la contractilité segmentaire du ventricule gauche est réalisée à l'échocardiographie transthoracique (ETT). L'examen est composé de plusieurs paliers progressifs de stress suivis d'une période de récupération. Il s'agit d'un examen fiable (sensibilité d'environ 85%, spécificité de 90%, valeur prédictive positive de 90%, et valeur prédictive négative de 90–95%), avec un risque de complications sévères en cas d'utilisation de la dobutamine inférieure à 0.3%.[9-15] Ces rares complications sévères sont essentiellement rythmiques.[9,10]

Nous présentons un cas d'infarctus du myocarde compliqué d'œdème aigu du poumon et de collapsus cardio-vasculaire au cours d'une échocardiographie de stress à la dobutamine.

Observation

Patient de 55 ans, diabétique de type 2 connu depuis 7 ans et bien équilibré sous metformine et glibenclamide était adressé dans notre service pour la recherche d'une ischémie myocardique silencieuse. Il n'était ni hypertendu, ni tabagique, ni obèse. Il n'y avait pas non plus de notion d'athérothrombose. Il présentait cependant un passé récent de douleur thoracique à type de gêne sans facteur déclenchant retrouvé. Sa tension artérielle était à 135/90 mmHg aux deux bras, le poids à 70 kg la taille à 1.78 m (IMC à 22.1 kg/m^2).

L'examen clinique cardio-vasculaire était normal. Il n'y avait pas de dyslipidémie, la fonction rénale était normale et le dosage de la microalbuminurie était négatif. L'électrocardiogramme de surface de repos était également normal de même que l'écho-Doppler cardiaque. L'épreuve d'effort réalisée sur tapis roulant était sous maximale négative. Une échocardiographie de stress à la dobutamine était alors programmée. L'examen est réalisé en palier de stress progressif de 10 µg/kg/min.

Au début du deuxième palier (20 µg/kg/min), est apparu un trouble de la cinétique segmentaire du ventricule gauche à type de dyskinésie de la paroi inféro-latérale et septale et une hypokinésie sévère antéro-latérale. Ces troubles de la cinétique segmentaire étaient accompagnés d'une douleur angineuse et d'un sous décalage du segment ST de 3 mm en antéro-septo-apical. Il y avait une augmentation concomitante de la tension

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artérielle à 200/130 mmHg et une installation rapide d'un œdème aigu du poumon (OAP) qui a nécessité l'administration de trinitrine en sublinguale et de 2 ampoules de furosémide 20 mg en IVD.

Puis la tension artérielle est devenue imprenable (collapsus cardio-vasculaire) d'où un remplissage vasculaire a été réalisé puis le patient hospitalisé pendant cinq (05) jours. Le seuil ischémique était de 0.97 et le score de contractilité segmentaire de 1.47. La troponine I était augmentée à 2.4 ng/l (soit 240 fois la normale). L'évolution était marquée par un amendement de la douleur et une normalisation du sous-décalage.

Après la phase critique le traitement était constitué d'énoxaparine 0,7 ml toutes les 12 heures, clopidogrel 75 mg en dose de charge (4 comp) puis 1 comp/jour, ramipril 5 mg: 1 comp/jour, atorvastatine 20 mg: 1 comp/jour, acide acétyl salicylique 100 mg: 1 sachet/jour, metformine 1 000 mg: 1 comp toutes les 8 heures et glybenclamide 5 mg: 1 comp/jour. Une coronarographie n'a pu être réalisée par insuffisance du plateau technique.

Commentaire

L'échocardiographie de stress a des indications précises et selon les recommandations conjointes de la société française de cardiologie (SFC) et de l'Association Française pour l'Etude du Diabète et des maladies métaboliques (ALFEDIAM),[16] notre patient n'avait pas d'indication de recherche d'ischémie silencieuse. En effet, il s'agit d'un patient jeune (moins de 60 ans), sans antécédents d'athérothrombose, sans microalbuminurie, sans HTA ni dyslipidémie et un diabète de moins de 10 ans. Néanmoins, l'antécédent de douleur thoracique atypique chez un patient diabétique a conforté notre option.

En effet chez le diabétique, les douleurs angineuses sont parfois sourdes. Chez ce type de patient, il existe une altération de la microcirculation et une dysfonction endothéliale qui pourraient expliquer la survenue d'un infarctus de stress myocardique.[17] Au cours de l'EDS, l'administration des drogues utilisées pour la réalisation de l'examen peut modifier les paramètres hémodynamiques mais non de manière significative.[18] Une mise en observation voire une hospitalisation peut être nécessaire lorsque les paramètres hémodynamiques de base ne sont pas obtenus à la récupération.

Quelques articles décrivent des infarctus du myocarde liés à la réalisation de l'EDS.[19,20] La survenue de l'IDM peut être immédiate[20,21] ou retardée jusqu'à deux heures après l'examen[19] et la négativité de l'examen n'empêche pas la survenue de l'IDM. Le mécanisme impliqué est le plus souvent une dissection coronaire ou une thrombose coronaire[22] mais le spasme coronaire est aussi évoqué.[17] Toutes les coronaires peuvent être concernées. Une revascularisation par angioplastie (ou pontage) est le plus souvent nécessaire[17,18,23] mais dans notre cas la coronarographie n'a pu être réalisée par insuffisance du plateau technique.

Conclusion

L'échocardiographie de stress est un examen jugé inoffensif et sûr. Néanmoins, sa réalisation doit être entourée de moyens de réanimation efficaces. Une mise en observation voire une hospitalisation pourrait être nécessaire en cas de complication comme ce fut le cas de notre patient.

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Case Report

Peripartum cardiomyopathy and familial dilated cardiomyopathy: a tale of two cases

K TIBAZARWA, K SLIWA, A WONKAM, BM MAYOSI

Abstract

Peripartum cardiomyopathy (PPCM) is a form of pregnancy-related heart failure that is associated with considerable morbidity and mortality. Most patients present with acute postpartal heart failure that otherwise resembles the clinical presentation of dilated cardiomyopathy (DCM). There is increasing recognition that PPCM may be due to genetic factors in a significant proportion of cases. There is evidence that at least 7% of cases of PPCM may be part of the spectrum of familial DCM. We report on two cases of PPCM, with relatives demonstrating familial DCM, both patients displaying autosomal dominant patterns of inheritance, and showing severe cardiomyopathy among proband and affected relatives. Family screening for familial DCM should be indicated in all cases of unexplained PPCM.

Keywords: peripartum cardiomyopathy, genetics, familial dilated cardiomyopathy, Africa

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Peripartum cardiomyopathy (PPCM) causes heart failure in women of child-bearing age. We describe two African patients with PPCM, diagnosed according to standard criteria,[1] who underwent comprehensive screening of first-degree relatives and were found to have familial disease. Informed consent was obtained from both patients and the study protocol conformed to the ethical guidelines of the 2008 Declaration of Helsinki as reflected in *a priori* approval by the human research ethics committee of the University of Cape Town.

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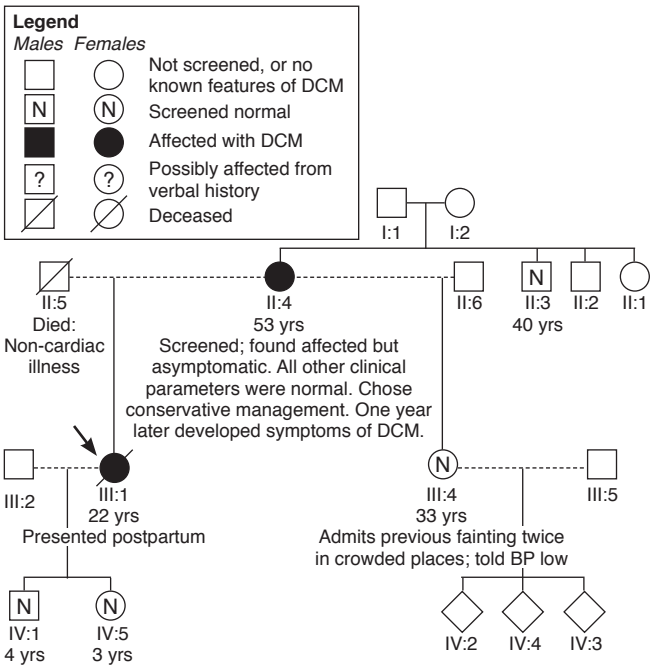
Case report 1

A 22-year-old mother of two presented 27 days postpartum with one week of symptoms and was diagnosed with PPCM. Despite treatment, she died at home within six months. Family screening found her mother to have asymptomatic dilated cardiomyopathy (DCM) (Fig. 1).

After opting for conservative management, the mother developed symptomatic DCM a year later, presenting in florid heart failure. Cardiac catheterisation and other investigations excluded coronary artery disease (CAD). The index case's half-sister admitted to a history of dizziness, low blood pressure and occasional fainting episodes in crowds but had no echocardiographic evidence of DCM.

Case report 2

A 23-year-old mother of two presented two months postpartum with PPCM. Family history revealed an unspecified heart condition in her mother, who died shortly after a cerebrovascular accident at age 60 years (Fig. 2). Her sister apparently developed heart failure four years after her first delivery at 19



NB. Dotted lines imply partners that never married

Fig. 1. Pedigree of index case (arrowed) with peripartum cardiomyopathy with familial disease (Family I). (DCM, dilated cardiomyopathy)

years of age and deteriorated after the birth of her second child 10 years later. This sister soon suffered a stroke and died one year after the second childbirth.

Active family screening revealed symptomatic DCM in her 39-year-old brother, without CAD; and asymptomatic left ventricular (LV) systolic dysfunction in her 22-year-old sister. Screening one elder sister showed Wolf-Parkinson-White syndrome.

These two cases of PPCM have at least one family member with DCM, and therefore meet the definition of familial cardiomyopathy.[2] The presentation in both cases is compatible with autosomal dominant inheritance.

PPCM and idiopathic DCM

The distinction of PPCM from idiopathic DCM may be difficult because both conditions are characterised by LV dysfunction with no apparent cause. Indeed, some investigators have proposed that PPCM may simply be idiopathic DCM manifesting in late pregnancy, this being a time when the haemodynamic changes of pregnancy could overwhelm the heart.[3] Along this hypothesis, increased preload leads to LV dilatation and cardiac insufficiency, a theory partly supported by earlier studies in which a number of cases presented in the last month antepartum or immediately postpartum.

However, such theory is not supported by studies showing that PPCM with no gestational hypertension present on average at two months postpartum,[4-6] having developed symptoms within two months postpartum.[6,7] By this time, these haemodynamic changes of pregnancy would have ceased.[4] However, cohorts with predominantly postpartum-onset PPCM display prognoses similar to those of idiopathic DCM, with far slower recovery than in PPCM phenotypes with predominantly gestational hypertension.[1,7]

Even though most women with asymptomatic or mildly symptomatic idiopathic DCM tolerate pregnancy uneventfully,[8] as with other pre-existing heart disease, any subclinical cardiomyopathy may be associated with the worsening of symptoms in the second trimester of pregnancy when the haemodynamic stress on the heart is maximal.[4] However, recent attempts to broaden the traditional gestational period defining PPCM[6] have renewed the controversy. Clear consensus on case definition is vital before clinical and epidemiological patterns can be reliably described.

Studies show 20–50% of all idiopathic DCM cases to have familial disease.[9-11] Although women have been shown in some studies to be equally affected as men,[9,12] more studies suggest a male predominance.[10] However, less than a handful of studies report on the incidence and outcomes of pregnancy in women with familial DCM.[8] To the best of our knowledge, no study has systematically investigated all immediate relatives of PPCM patients to ascertain the prevalence of familial DCM among these patients.

PPCM and familial DCM

There have been several reports of familial disease in PPCM.[1,13,14] Two Western studies and one South African case series suggest that a subset of PPCM patients may be part of the spectrum of familial DCM presenting in the peripartum period.[10,14,15] Surprisingly, PPCM patients in each of these two Western studies almost uniformly presented postpartum, with only one case in each study presenting within the last six weeks of term pregnancy (i.e. only one to two weeks from the

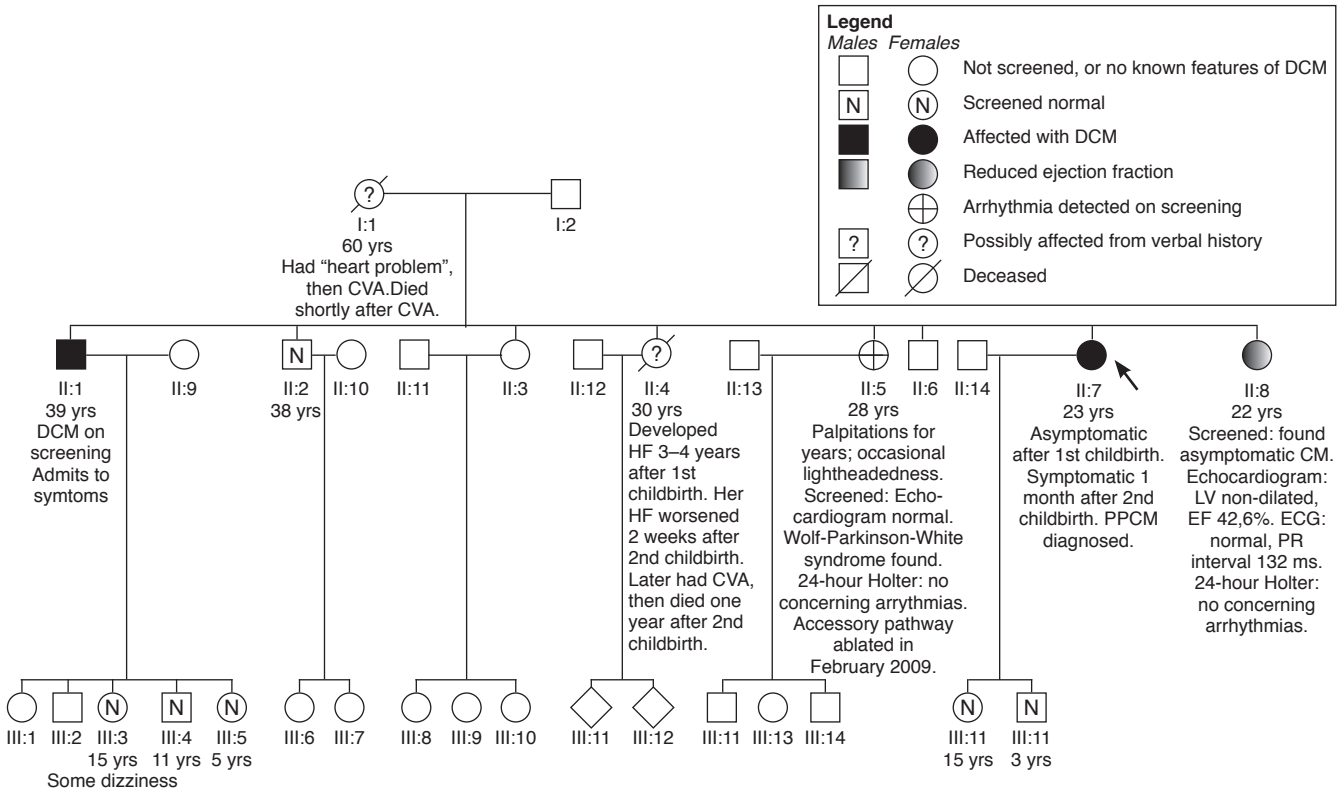


Fig. 2. Pedigree of index case (arrowed) with peripartum cardiomyopathy with familial disease (Family II).

traditionally defined time of onset of PPCM).[14,15] These studies were weakened by their exclusion of patients who recovered LV function within the first year, thereby cutting out 25–50% of the spectrum of PPCM patients and favouring the possibility that only FDCM phenotypes were retained, as the latter rarely recover LV function.

Nonetheless, these findings raise two pertinent questions. First, other than postulations of late-pregnancy oxidative stress triggering the PPCM phenotype, how did these putative familial DCM cases surpass the expected time of presentation for pre-existing heart disease in the second trimester? Second, could the genetic polymorphisms or mutations identified so far in PPCM cases with familial disease be a co-incidental finding, while the real culprits for PPCM phenotypes lie in other genetic mutations inadequately sought for beyond those known to cause familial DCM?

Familial DCM manifests in an age-dependent manner with incomplete disease penetrance.[9] Therefore, in the absence of long-term, population-based studies, answering our second question will remain a challenge. As heterogeneous as familial DCM is, over 40 defective genes have been associated with inherited DCM, although they account for a minority of familial DCM cases.[16]

Genome-wide association studies (GWAS) may succeed in identifying pathogenic mutations for PPCM. The only known attempt at GWAS in PPCM patients was done in Utah,[17] and revealed 10 single-nucleotide polymorphisms (SNPs) that may play a role in the pathogenesis of PPCM.[17] Of these, one SNP (located on chromosome 12) demonstrated genome-wide significance for PPCM, likely triggering disease through abnormal immune modulation.[17] The strength of the study lies in its efforts to exclude patients with co-morbidities that would confound the diagnosis of PPCM, and for screening a variety of controls, including post-menopausal controls,[17] to enable discovery of PPCM-associated loci relevant to the at-risk population of pregnant/potentially pregnant females.[17] Furthermore, the authors went as far as to describe 30 other SNPs which appeared to predict the absence of PPCM,[17] suggesting a route for the exploration of protective mechanisms to PPCM.

Recent advances favouring PPCM as an independent disease shows *in vitro* and *in vivo* evidence of an abnormal 16-kDa prolactin pathway intertwined with oxidative stress.[18] However, given that oxidative stress, together with signal transducer and activation of transcription factor-3 (STAT-3) depletion, as implicated in this model may be common to most forms of severe heart failure, including idiopathic DCM,[19] the only component to this pathway that might remain unique to PPCM is that fuelling production of the 16-kDa fragment of prolactin. However, linking this abnormal prolactin pathway exclusively to PPCM would require proof of its absence in women with familial DCM, including relatives who subsequently fall pregnant and deteriorate.

Despite the GWAS described above[17] having failed to find any SNP or other variation on the STAT-3 gene to account for PPCM, it introduced the possibility of an association between polymorphic variations (SNPs) on the STAT-5 gene and PPCM. This is important because STAT-5 is a known culprit in idiopathic DCM,[19] making the thought of it playing a role in the development of PPCM an interesting possibility.

Novel data further suggest that imbalances between cardiac pro-angiogenic factors PGC-1α and vascular endothelial growth factor (VEGF), and anti-angiogenic factors such as the VEGF inhibitor soluble Flt1 may result in PPCM, and that this association is more profound in the presence of gestational hypertension and multiple pregnancy.[20] If indeed these mechanisms become validated, it would be essential to establish any genetic bases for these abnormalities.

Conclusion

There are several lessons to be learned from this detailed family study of two cases with PPCM. First, we emphasise the need for family screening of PPCM and idiopathic DCM patients,[10] with long-term follow up of screened persons, particularly of females of child-bearing age. There is a need for well-structured incidence studies of PPCM and idiopathic DCM, with baseline echocardiograms of primary relatives (irrespective of symptoms), pre-pregnancy echocardiography of all women being followed up (irrespective of underlying co-morbidities), and follow up with echocardiography every two to five years.[21] This exercise could mould routine practice, given the high prevalence of familial DCM, its lethal course, and the suggested benefits of treating asymptomatic relatives with LV dysfunction.[11]

Aside from the GWAS reported several years ago,[17] the search for genetic abnormalities in PPCM has remained narrowed towards screening for mutations (or SNPs) associated with familial DCM. It would be recommended to expand on the reported GWAS by testing the clinical impact of the SNPs already suspected to be associated with PPCM.[17] Furthermore, in the hope of identifying new SNPs accountable for PPCM through target-gene search or GWAS, it may be logical to start comparing genotypes of extreme phenotypic presentations of both PPCM and idiopathic DCM (i.e. mild versus severe) within and across their respective diagnostic groups.

In addition, in the search for PPCM-specific genetic abnormalities, the co-existence of the abnormal 16-kDa prolactin cascade would need to be evaluated in familial DCM patients who deteriorate in pregnancy, and the genetic abnormalities programming this abnormal pathway further explored. Lastly, next-generation sequencing (NGS) is a recently developed, massively parallel, large-scale sequencing technology that has been used for rapid gene cloning and mutation detection. Taking advantage of the larger size of families in Africa, NGS with exome selection could be used to identify the causative genes and to improve both genetic and clinical delineation of DCM and PPCM.

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Case Report

Spontaneous retrograde dissection of the ascending aorta in a patient with a bicuspid aortic valve

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Abstract

Bicuspid aortic valve (BAV) is a congenital anomaly associated with structural weakness of the aortic wall. Sudden onset of symptoms in patients with BAV, such as sudden severe back pain, and pulse inequality between the extremities or tension disparity should alert clinicians to acute aortic syndromes, as they require prompt diagnosis and management. Retrograde aortic dissection, which is a rare form of acute aortic syndrome, is an uncommon life-threatening entity and may produce atypical computed tomography (CT) or magnetic resonance imaging findings, leading to difficulty in diagnosis. We report on a 51-year-old male patient with BAV and spontaneous retrograde ascending aortic dissection. CT findings were confusing and the diagnosis was made via transoesophageal echocardiography. After the diagnosis, the patient was treated with a modified Bentall procedure. He did not have any complications and was stable four months after the operation.

Keywords: spontaneous, retrograde ascending aortic dissection, transesophageal echocardiography, bicuspid aortic valve

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Retrograde dissection of the ascending aorta is a rare disease that usually arises as a complication of some invasive manoeuvres.[1,2] Mostly the entry tear starts in the descending aorta and expands retrogradely to the ascending aorta.[3] The spontaneous form is extremely rare and the aetiology is controversial.

A bicuspid aortic valve is the most common congenital heart disease, with an incidence rate of 1.3% in the general population.[4] In patients with a bicuspid aortic valve, one of the suggested mechanisms of aortic dissection is associated constitutional weakness of the aortic wall.[5] Valvulopathy is the most frequent complication, however, and in Marfan syndrome, aortopathies may be associated as well.[6,7] The latter is important as it may lead to aortic dissection and sudden death.[8]

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We report here on a 51-year-old male patient with a bicuspid aortic valve and spontaneous dissection of the retrograde ascending aortic. To the best of our knowledge, spontaneous retrograde dissection limited to the ascending aorta in a patient with a bicuspid aortic valve has not been reported in the literature before.

Case report

A 51-year-old male patient presented with retrosternal angina and severe back pain for the previous eight hours. He was referred from another centre where aortic dissection was suspected, and a computed tomography (CT) scan was performed. There was no sign of aortic dissection but an ascending aortic aneurysm was recognised.

On physical examination, his blood pressure was 120/60 mmHg on the left arm and 115/60 mmHg on the right. His pulse was 95 beats/minute. The lung examination was normal. There was no difference between the right and left side pulses. He had reported no trauma or back pain during the last few days. He was not a smoker and had a clear medical history.

Cardiac auscultation revealed grade 2/6 diastolic murmur in the aortic area. His electrocardiogram (ECG) and cardiac markers were normal. A telecardiogram revealed a normal cardiothoracic index but there was a slight mediastinal widening. Aortic dissection was suspected, however CT angiography of the aorta showed a 50-mm aortic aneurysm in the ascending aorta without any signs of dissection (Fig. 1).

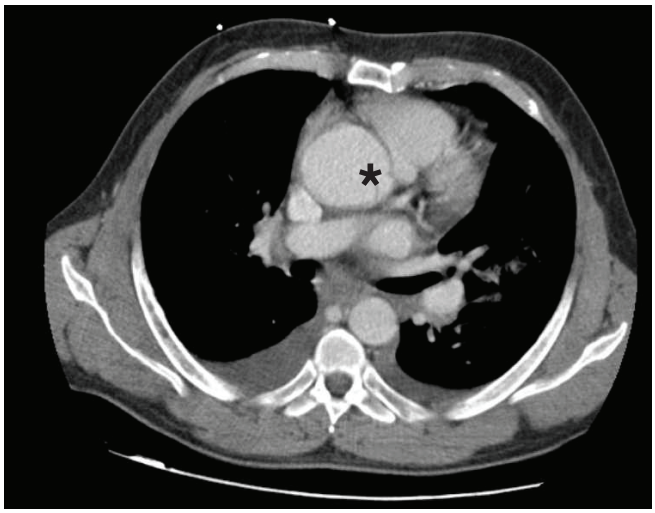

Fig. 1. A CT angiography scan with contrast administration was not demonstrative of aortic dissection. The faint intra-aortic line seemed more like an artifact (asterisk).

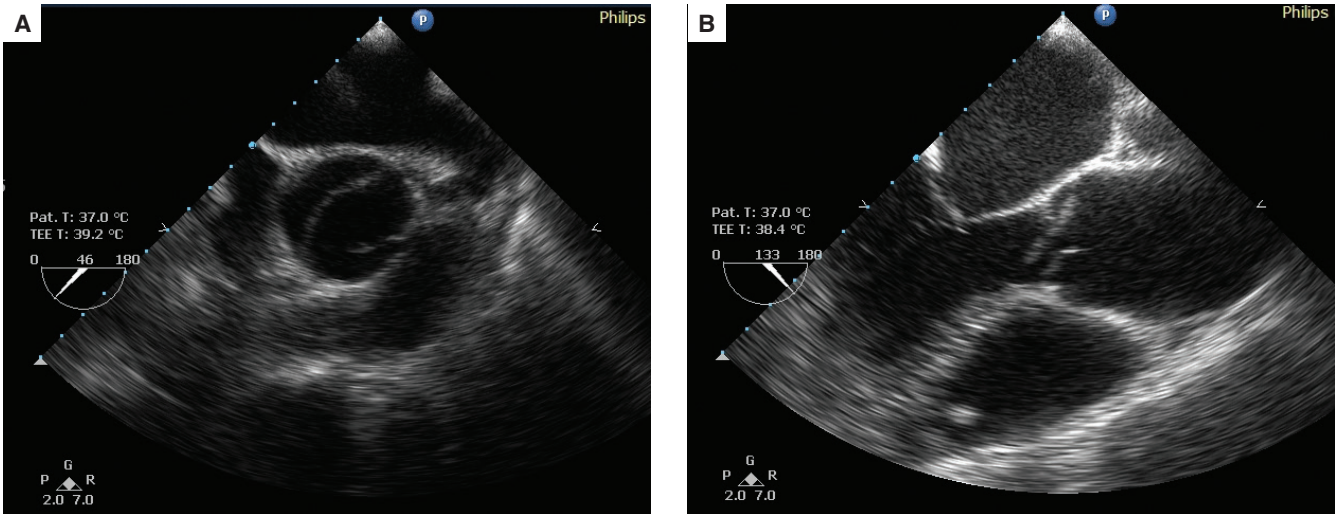

Fig. 2. A. Transoesophageal echocardiography depicting the bicuspid aortic valve. B. Transoesophageal echocardiography demonstrating an accessory valve-like structure 2 cm above the aortic valves. Findings were suggestive of an atypical form of aortic dissection in the patient with a bicuspid aortic valve.

The radiologist, cardiovascular surgeon and cardiologist re-examined the CT images due to remaining uncertainty. The radiologist was adamant about the radiological diagnosis and emphasised there were no typical signs of a dissection flap. However he agreed on second review that there was a faint intra-aortic double line in the short segment of the ascending aorta just above the valves but it seemed more like an artifact than an intra-aortic flap.

Due to uncertainty, the patient was sedated and transoesophageal echocardiography (TEE) was performed. TEE demonstrated an accessory valve-like structure in the ascending aorta, 2 cm above the bicuspid aortic valves (Fig. 2A, B). There was severe aortic valve insufficiency. It was reported to be an atypical form of aortic dissection.

The patient was scheduled for aortic valve and ascending aorta replacement. During the operation, the dilated aortic root and proximal ascending aorta were observed but the distal ascending and arcus aorta were in normal alignment. There was a retrograde spiral dissection of the ascending aorta (approximately 270 degrees of the circumference of the aorta was involved) with an entry tear 2 cm above the coronary ostia, extending to the proximal aortic root (Fig. 3). The aortic wall was secure at the distal part of the ascending aorta.

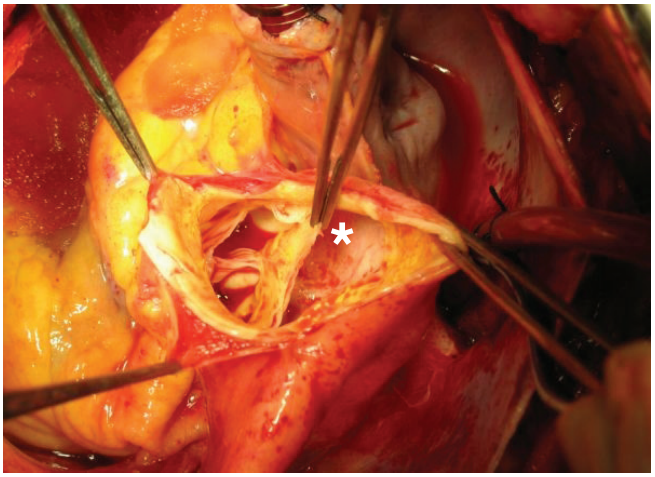

Fig. 3. Intra-operative view showing the entry tear of the dissection flap in the distal part of the ascending aorta (asterisk). Note the bicuspid aortic valves.

The aortic valve and proximal ascending aorta were resected and a modified Bentall procedure was performed using a 25-mm composite graft. The patient had no complications and was stable four months after the procedure.

Discussion

Dilation of the ascending aorta in children with bicuspid aortic valves has been previously described in some cohorts of children.[9,10] Moreover, adults with bicuspid aortic valves are shown to be at greater risk for progressive aortic dilation independent of valve function.[11] The exact reason is unknown but there are some suggested physiopathological mechanisms.

The neural crest is a remarkable structure. Some studies have shown that the neural crest plays an important role in the development of cardiac and a variety of non-cardiac structures. The cardiac structures derived from the neural crest involve the outflow tract of the heart and the aortic arch system. Mal-development of neural crest cells are thought to be responsible for the combined occurrence of outflow tract (e.g. bicuspid aortic valve), aortic arch (e.g. coarctation) and non-cardiac anomalies.[12]

Of interest, another important study demonstrated a strong association between endothelial nitric oxide synthase (eNOS) deficiency and the presence of a bicuspid aortic valve.[13] They reported that mice lacking functional eNOS demonstrated a high incidence of bicuspid aortic valves.

This evidence suggests that a patient with a bicuspid valve should be carefully monitored for aortic pathologies. Atypical forms of aortopathies such as spontaneous retrograde dissections may occur, and both clinicians and radiologists should be on the alert. Diagnosis may require more accurate examination.

Conclusion

It appears that the transesophageal echocardiogram is the gold standard of diagnostic procedures in cases of retrograde

aortic root dissection, as it has better accuracy compared to the CT scan. This marked advantage may partly arise from the direct application of this procedure by the clinician. TEE must be performed before the final decision to exclude acute aortopathies in patients with bicuspid aortic valves, especially when there is still a high clinical suspicion after a study such as CT angiography.

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Case Report

Ventricular tachycardia-based long QT without hypocalcaemia after use of ibandronic acid

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Abstract

Many drugs are known to cause lengthening of the QT interval. Ibandronic acid is a frequently used agent in the treatment of osteoporosis and is known to cause prolongation of the QT interval due to hypocalcaemia. However, no cases of long QT syndrome associated with ventricular tachycardia (VT) with a serum calcium level within the normal limits have been reported in the literature. We report on a case of a VT-based long QT syndrome associated with the use of ibandronic acid.

Keywords: long QT, ventricular tachycardia, ibandronic acid, cardioversion

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Long QT syndrome is important because it triggers life-threatening arrhythmias and poses the risk of sudden cardiac death. Long QT syndrome can be divided into two forms: congenital and acquired.[1] Anti-arrhythmic agents, non-sedative antihistamines, antipsychotic agents, and gastrointestinal prokinetic agents are the most widely encountered causes of acquired long QT syndrome.[2]

Bisphosphonate agents are widely used in the treatment of osteoporosis.[3] Ibandronic acid is a bisphosphonate agent with no significant reported cardiovascular side effects. This report presents a case of acquired long QT syndrome that degenerated into malignant arrhythmia associated with the use of ibandronic acid.

Case report

A 57-year-old female patient with palpitations came to the external centre in a serious condition. She was transferred to our centre after starting medical cardioversion with intravenous

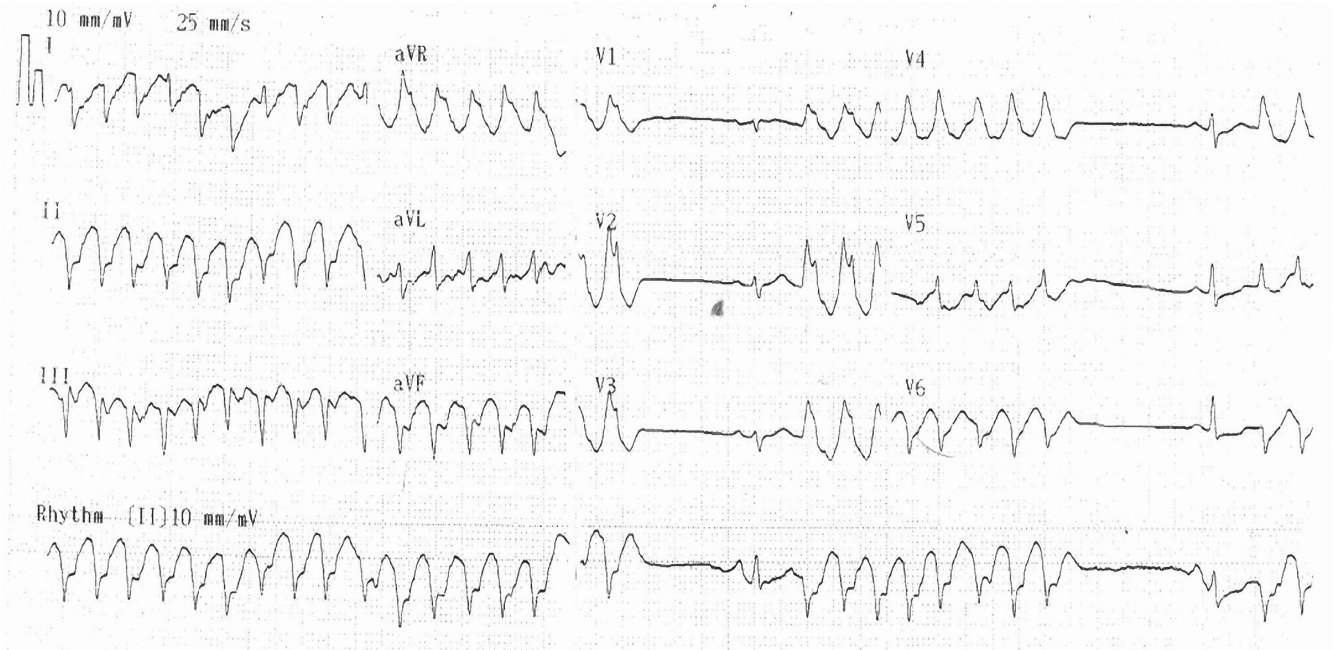

Fig. 1. Monomorphic ventricular tachycardia and captured sinus beat seen on the surface 12-lead ECG, taken at the first admission.

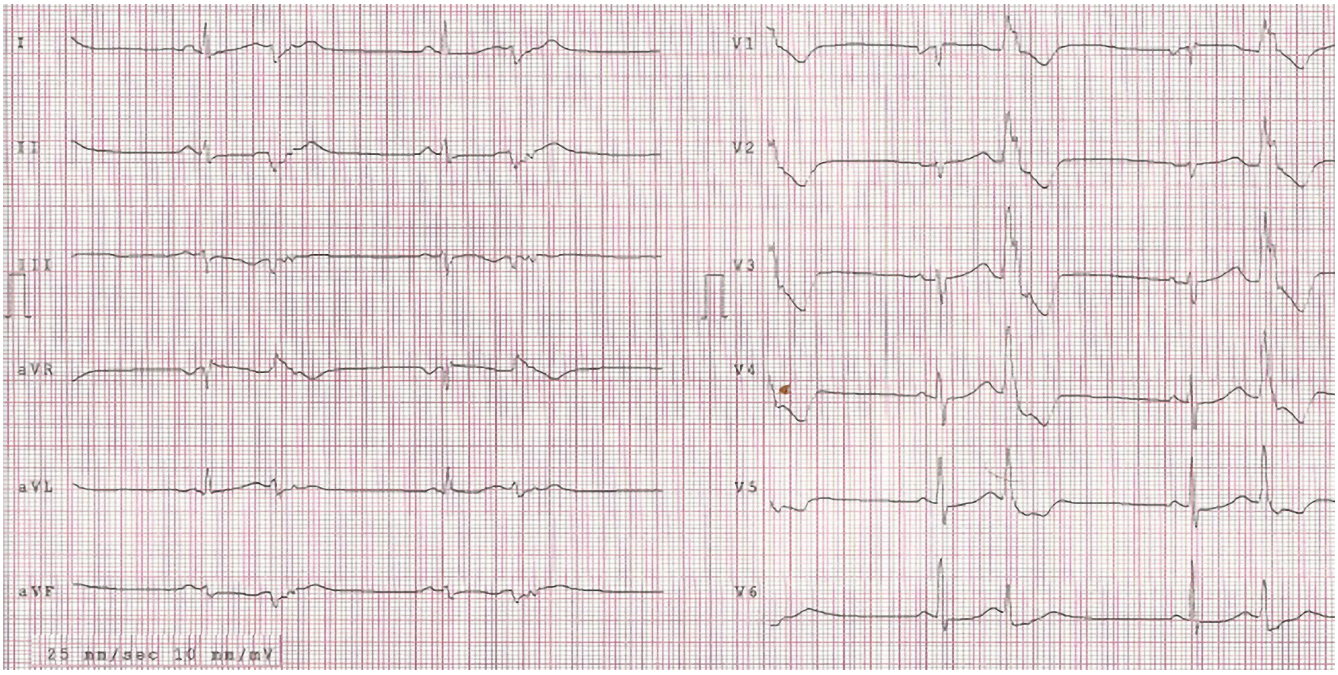

Fig. 2. Normal sinus rhythm with ventricular bigeminy extrasystole and prolonged QT interval, measured as 0.53 seconds, after medical cardioversion.

amiodarone upon detection of ventricular tachycardia (VT) on electrocardiography (ECG) (Fig. 1).

At the first admission to our hospital, the patient had a normal sinus rhythm with ventricular bigeminy extrasystole, and her corrected QT (QTc) interval was measured at 0.53 seconds on ECG (Fig. 2). She had no relevant family history and no cardiac risk factors, except for hypertension. She had no coronary artery disease, according to a coronary angiography performed seven months earlier.

We learnt the reason for the coronary angiography had been for atypical exertional chest pain. The patient had previously used bisoprolol 5 mg, valsartan 160 mg and amlodipine 10 mg for hypertension. In addition, she had received ibandronic acid treatment for osteoporosis for two weeks.

During the physical examination, the patient's blood pressure and cardiac pulse rate were 129/62 mmHg and 63 beats/min, respectively. No pathological sound was heard during pulmonary and cardiac auscultation. Serum potassium, calcium and magnesium levels and other routine biochemical measurements were in the normal ranges. No significant increase was detected during cardiac enzyme monitoring, so VT associated with coronary ischaemia was not a primary consideration.

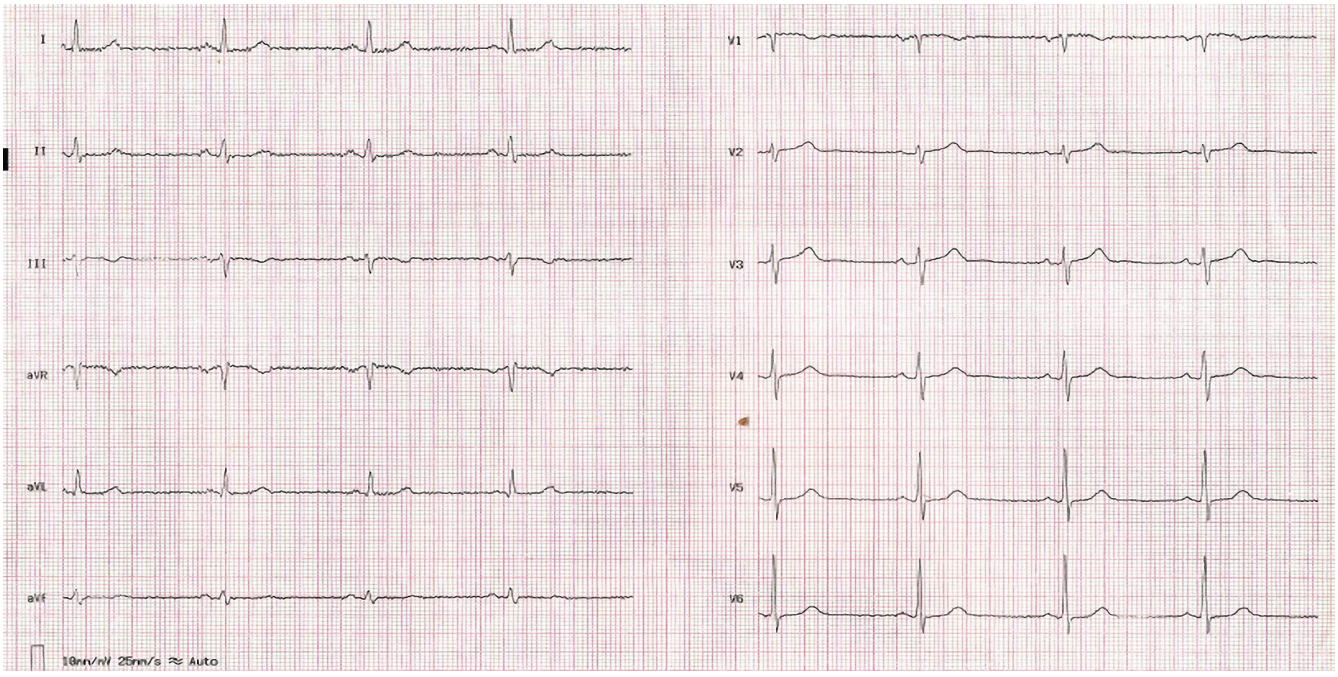

Fig. 3. Corrected QT interval returned to normal, measured as 0.42 seconds, two weeks after discontinuation of ibandronic acid.

With transthoracic echocardiography, the ejection fraction of the left ventricle was measured at 60% and medium tricuspid valve insufficiency was detected. Additionally, a detailed family history of the patient, particularly with regard to sudden cardiac death, was taken. Cardiological examination including echocardiography and ECG analysis of first-degree relatives of the patient was also done.

Acquired long QT syndrome associated with ibandronate was the primary consideration. Acetylsalicylic acid, subcutaneous enaxoparine and bisoprolol were administered to the patient, and ibandronic acid was discontinued. Amiodarone therapy had also been stopped at the first admission to our hospital due to the termination of the patient's VT attack.

ECG monitoring was performed regularly on the patient for two weeks after the discontinuation of ibandronic acid. It was observed that ventricular extrasystoles disappeared and the QTc interval returned to normal, measured at 0.42 seconds (Fig. 3). Finally, no VT was induced with programmed ventricular stimulation during a diagnostic electrophysiological study after the normalisation of the QTc interval.

Discussion

The top limit for the duration of the QTc interval according to heart rate is usually given as 0.44 seconds, however, it can be 0.46 seconds in men and 0.47 seconds in women.[1] Prolongation of the duration of the ventricular action potential is recognised as prolongation of the QT interval on superficial ECG and can cause torsades de pointes, a life-threatening arrhythmia.[2]

Acquired long QT syndrome can be induced by anti-arrhythmic agents, such as quinidine, procainamide, sotalol, amiodarone and disopyramide; tricyclic antidepressant drugs; non-sedative antihistamines, such as astemizol and terfenedine; and antibiotics, such as erythromycin and pentamidine. Acquired long QTc may also be caused by electrolyte abnormalities such as hypokalaemia, hypocalcaemia and hypomagnesaemia; fasting; lesions on the central nervous system; apparent bradyarrhythmias; cardiac ganglionitis; and mitral valve prolapse.[1]

In our case, there was no previously known structural cardiac disease, and no electrolyte abnormality was detected on admission. Acute ischaemia was not considered because the patient's cardiac enzymes were within normal limits, and no lesions had been detected in a recent coronary angiography. Based on the history of taking ibandronate for two weeks and no other drug that prolongs the QT interval except for amiodarone, whose half-life may be up to 100 days,[4] we diagnosed the patient with VT-based acquired long QT syndrome associated with ibandronate.

Bisphosphonate agents are widely used in the treatment of osteoporosis, Paget's disease and hypercalcaemia.[3-5] They are inorganic pyrophosphate analogues that act as endogenous regulators of calcium metabolism. Ibandronate is a bisphosphonate derivative preferred primarily for the treatment of hypercalcaemia and osteolytic bone disease.[5] The wide use of bisphosphonates necessitates investigation of their relationship with cardiovascular diseases.[6]

Much research related to the cardiovascular safety of bisphosphonates has been conducted. A published analysis stated that zoledronic acid, which is a bisphosphonate derivative, increased the incidence of atrial fibrillation and that no significant difference in arrhythmia potential was found between other bisphosphonate derivatives and placebos. Furthermore, no increase was established in cases of death, stroke and other non-arrhythmic cardiovascular events.[7]

In another study in which ibandronate was administered to 6 830 patients and a placebo to 1 924 patients, no increased incidence in atrial fibrillation or other serious cardiovascular disease was observed after either oral or intravenous administration of ibandronate.[8] Bisphosphonates may induce abnormalities of electrolytes, and ibandronate is more potent than other bisphosphonates in promoting the development of hypocalcaemia. Clinical findings may be associated with the development of hypocalcaemia and electrocardiographically long QT.[9]

No serious cardiovascular cases associated with ibandronate use have been reported in the literature. However, pathologies such as abnormalities of electrolytes, ischaemia and structural heart disease that may cause acquired long QT syndrome were not detected in our case. The patient was thought to have acquired long QT syndrome and accordingly, ventricular tachycardia associated with ibandronate use, even though the serum calcium level was normal.

Intravenous magnesium, atrial or ventricular pacing control and cardioversion are among the first methods to select for patients who have developed acquired long QT syndrome and VT. It is necessary to avoid any agents that cause long QT.[1] Since ventricular arrhythmia is associated with reversible causes, there are no indications for implantable cardioverter-defibrillator (ICD).[10]

In our case, after medical cardioversion with amiodarone, ibandronate therapy, which can cause long QT syndrome, was discontinued and electrolytes were monitored frequently to prevent an imbalance that could induce ventricular arrhythmias. No temporary pacing or repeated cardioversion was required for our patient due to haemodynamic stabilisation throughout hospitalisation.

During follow up, the patient's QTc interval returned to the normal range and no symptoms developed. In addition, VT was not induced with programmed ventricular stimulation during diagnostic electrophysiological study after the normalisation of the QTc interval.

Conclusion

ECG monitoring should be performed regularly on patients treated with bisphosphonates such as ibandronic acid. As in our case, ibandronic acid may cause VT after prolongation of the QT interval, even without the development of any electrolyte abnormality.

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