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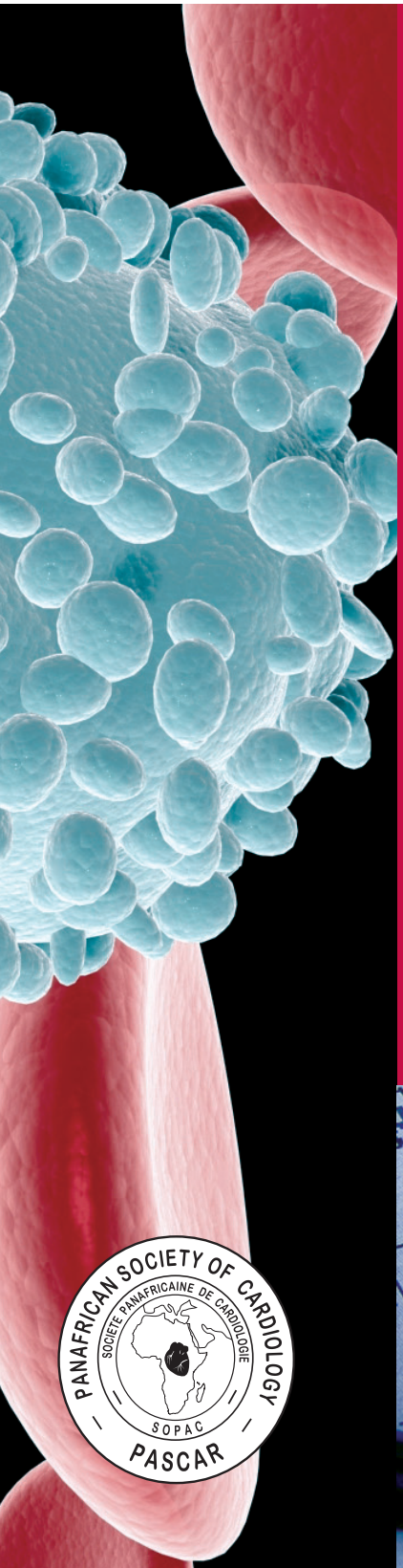

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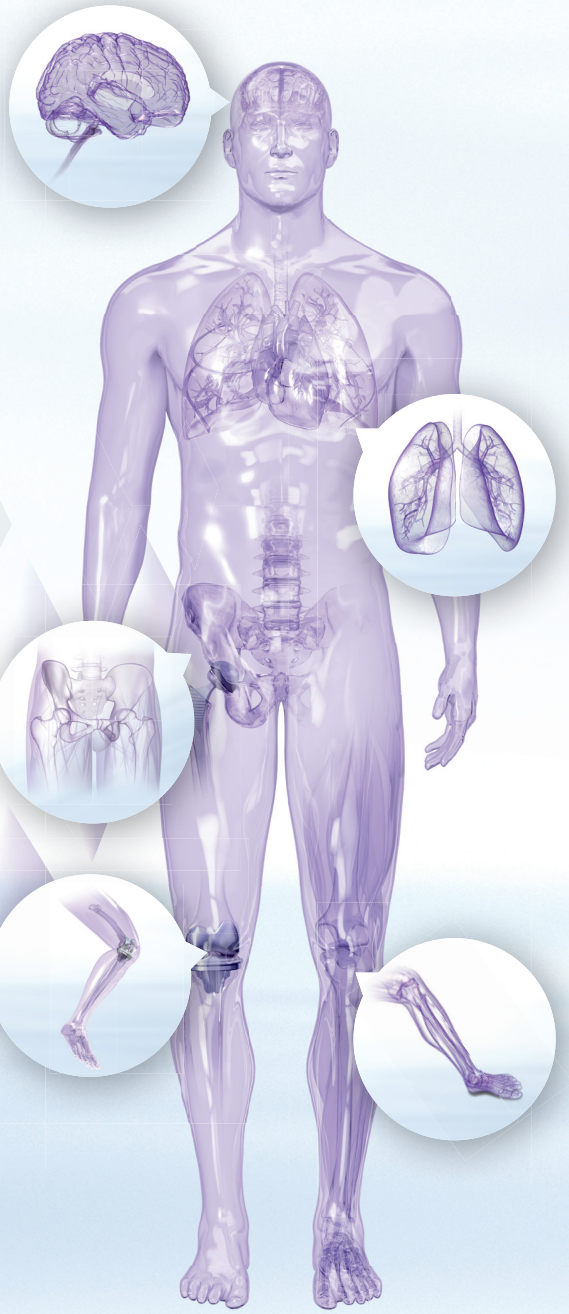

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From the Editor's Desk

This issue contains useful information on patterns of disease presentation in Africa. Grimaldi and colleagues (page 204) document the pattern of structural heart disease causing heart failure in patients presenting to a tertiary hospital in Kampala. Many were young and suffered from rheumatic heart disease (RHD) and congenital heart disease (CHD). One suspects this was a highly selected group as the patients were identified during NGO missions, presumably aimed at identifying suitable candidates for surgery. Nonetheless the article reflects the importance of RHD as a cause of disability and death in the young in Uganda, as in many other parts of Africa, and emphasises the need for efforts to improve primary and secondary prevention of this eminently preventable disease.

Another aspect of the heart failure spectrum is presented by Ogah and colleagues (page 217). A registry of patients admitted to hospital with acute heart failure and followed for six months showed a pattern of disease different from that found in high-income countries. Patients were younger, the aetiology of the heart failure was most commonly hypertensive heart disease, and an ischaemic aetiology was uncommon. In another article investigating hypertensive heart disease, Ojji and colleagues (page 233) report that brain natriuretic peptide is useful in evaluating cardiac remodelling in African patients with hypertension.

Thrombolysis for acute ischaemic stroke is, I suspect, used much less frequently in Africa than in many other parts of the world because of resource constraints. It is helpful to learn from von Klemperer and co-workers (page 224) that predictors for the serious complication of intracranial haemorrhage, developed elsewhere, apply in an African setting, although it is important to recognise that the demographics of the population of Cape Town differ considerably from the rest of Africa.

PJ Commerford
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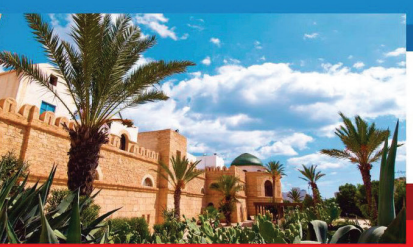

Cardiovascular Topics

Diagnostic value of plasma C-type natriuretic peptide levels in determination of the duration of mesenteric ischaemia

Sinan Demirtas, Oguz Karahan, Suleyman Yazici, Orkut Guclu, Ahmet Caliskan, Orhan Tezcan, Celal Yavuz

Abstract

Objective: Mesenteric arteries release C-type natriuretic peptide (CNP), which hyperpolarises vascular smooth muscle. We measured the levels of this peptide after inducing mesenteric ischaemia over a series of time intervals, so as to determine its predictive value in demonstrating the severity of ischaemia in a rat model.

Methods: A total of 32 rats were allocated to four groups containing eight rats each. Basal CNP reference levels were measured in the control group, which was not exposed to any intervention. In groups I, II and III, mesenteric ischaemia was induced over three, six and nine hours, respectively, and plasma CNP levels were measured afterwards. Mesenteric ischaemia was induced by clamping the superior mesenteric artery.

Results: In comparison with the controls (2.38 ± 0.18 pg/ml), CNP levels were relatively lower in group I (2.54 ± 0.42 pg/ml). However, significant increases in plasma CNP levels were observed over longer periods of ischaemia in group II, at 5.23 ± 0.22 pg/ml, and in group III, at 6.19 ± 0.67 pg/ml ($p < 0.05$). A significant direct relationship was determined between plasma CNP levels and prolonged intervals of mesenteric ischaemia ($R = 0.56$, $p < 0.001$).

Conclusion: Measuring plasma CNP levels in patients with acute mesenteric ischaemia may be beneficial in estimating the time period over which the ischaemic injury has occurred.

Keywords: C-type natriuretic peptide, mesenteric ischaemia, ischaemia duration

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Acute mesenteric ischaemia (AMI) causes significant morbidity and mortality if not promptly diagnosed and treated. If medical interventions are delayed, the patient may sustain serious ischaemic injury leading to bowel necrosis, so large segments of bowel may require surgical resection. Often these patients have poor clinical outcomes and suffer from complications such as malnutrition.[1,2] Mesenteric ischaemia makes up 0.1% of all hospital admissions.[1] Even though technological advances have been made in diagnostic laboratory and imaging techniques, AMI remains fatal in 60% of patients diagnosed with this condition.[1,3]

Scientists have been investigating whether there are specific sensitive biomarkers that may indicate the presence of AMI.[2,4] Several endothelial markers have been identified as putative biomarkers that may reveal the severity and duration over which mesenteric ischaemia has been sustained.[5] However, markers that are effective enough for use in clinical practice have yet to be identified.

Natriuretic peptides, namely atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) function in maintaining fluid and electrolyte balance as well as blood vessel tone. CNP is released by vascular endothelial cells, and this biomarker's function in influencing vascular tone has been investigated.[6,7] It has been hypothesised that CNP is an endothelium-derived hyperpolarising factor (EDHF) that specifically affects the degree of resistance in the mesenteric arteries.[8] In this study, we aimed to investigate plasma CNP levels during early and advanced stages of mesenteric ischaemia so as to determine whether CNP levels are a good indicator of severity of AMI in a rat model.

Methods

The study protocol was created in accordance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals created by the university ethics committee. The rats were obtained and housed in the laboratory of the University's animal production unit. They were maintained in a controlled environment with 12-hour light–dark cycles, and the cages were kept at a constant humidity of 50 ± 5% and temperature of 22 ± 2°C.

A total of 32 male Sprague-Dawley rats between the ages of eight and 12 weeks and weighing 230 ± 30 g (mean ± standard deviation) were randomly allocated to four different groups. The induction of sedation was achieved with an intraperitoneal

injection of 130 mg/kg of ketamine (Ketalar, Pfizer) and 20 mg/kg of xylasine (Rompun, Bayer). Sedation was maintained with 50 mg/kg of ketamine hydrochloride so that the animals remained under anaesthesia during blood collection and superior mesenteric artery clamping.

Blood samples were obtained from the control group to determine basal CNP levels. A simple laparotomy was performed on the rats in groups I, II and III in order to clamp the superior mesenteric artery (SMA) and artificially create mesenteric ischaemia. The SMA remained clamped for three hours in group I, six hours in group II, and nine hours in group III. Blood samples were collected from the animals after the designated duration of induced mesenteric ischaemia without declamping, and then they were sacrificed. Several animals died during the procedure, including one in group II and three in group III, and they were subsequently excluded from the study. Plasma CNP levels were measured from the collected blood samples.

Biochemical analysis was as follows. Blood collection tubes containing citrate were used, and after the samples were obtained they were centrifuged at 4 000 rpm at 4°C for 10 minutes. The centrifuged samples were then transferred into Eppendorf tubes for storage at –80°C.

Commercially available radioimmunoassay kits (RIA) (C-type natriuretic peptide-22, Phoenix Pharmaceuticals, Belmount, CA, USA) were used to determine plasma CNP levels. One millilitre of plasma was eluted with a 1-ml volume of 60% acetonitrile mixed in a 1% trifluoracetic acid (TFA) solution for the solid-phase extraction step, as previously described by del Ray *et al.*[7]

After the remaining product was dissolved in 300–500 µl of assay buffer, 100 µl of the resulting mixture was used to perform the immunometric assay.[7] The average CNP recovery was calculated to be 74.8%.

Statistical analysis

Statistical calculations were performed with the SPSS software (SPSS version 15.0 for Windows, SPSS Inc., Chicago, IL USA). Data were expressed as the mean ± one standard deviation (SD). The Kolmogorov–Smirnov test was used to assess whether the data conformed to a normal distribution. A p-value < 0.05 was considered statistically significant. Significant differences between group means were assessed with one-way analysis of variance (ANOVA). Tukey's honest significant difference (HSD) was used as a *post hoc* test.

Results

In the control group, the mean plasma CNP level was 2.54 ± 0.42 pg/ml. A slight decrease in CNP level was observed in group I relative to the controls following three hours of induced mesenteric ischaemia [2.38 ± 0.18 pg/ml (p = 0.085)]. However, mean CNP levels were dramatically increased in group II (5.23 ± 0.22 pg/ml) compared to the controls and group I following six hours of mesenteric ischaemia (p = 0.001). Average CNP levels were even higher in group III (6.19 ± 0.67 pg/ml) relative to the controls and group I (p = 0.000) and group II (p = 0.036).

There was a significant positive correlation between plasma CNP levels and longer durations of induced mesenteric ischaemia (R = 0.56, p < 0.001). The CNP levels observed in each experimental group are summarised in Fig. 1.

Discussion

The findings of this study indicate that plasma CNP levels were relatively low during the initial stages of mesenteric ischaemia. However, CNP levels quickly elevated in response to longer durations of sustained ischaemic injury. These findings are promising because CNP levels may allow one to differentiate between early and late mesenteric ischaemia.

The initial reduction in CNP levels during the early hours of mesenteric ischaemia may have been due to systemic CNP regulatory pathways. On the other hand, elevated plasma CNP levels during the sixth and ninth hours of induced mesenteric ischaemia may signify delayed mesenteric endothelial resistance or a response compounded by progressively worsening mesenteric ischaemia.

CNP was first isolated from blood collected from the brain and was subsequently categorised into the natriuretic peptide family, which contains three molecules that have a particular 22-amino acid structure.[9] In later studies, it was reported that CNP may also be isolated from plasma samples obtained from the colon, lung, heart and kidneys.[9]

CNP is a unique endogenous ligand for natriuretic peptide B receptor (NPR-B) and is upregulated by transforming growth factor-β, which is an important vascular remodelling factor.[9,10] NPR-B is located on vascular smooth muscle and modulates vascular tone.[9,11]

CNP inhibited proliferation of endothelial and vascular smooth muscle cells in *in vitro* studies.[12] Additionally, CNP demonstrated anti-atherogenic properties via p-selection suppression, which regulates the recruitment of leukocytes and platelet–leukocyte transmission.[12]

It has been reported that CNP is released from endothelial cells in rat mesenteric vessels and activates endothelium-derived hyperpolarising factor (EDHF). EDHF then triggers potassium channel opening and NPR-B activation so that mesenteric vascular smooth muscle cells will hyperpolarise and relax.[13] Despite the important role that CNP plays in mesenteric vessel tone, the effects of CNP have not been previously studied in the setting of mesenteric ischaemia.

CNP produced anti-fibrotic and anti-proliferative effects via inhibition of cultured fibroblasts, and reduced tissue growth

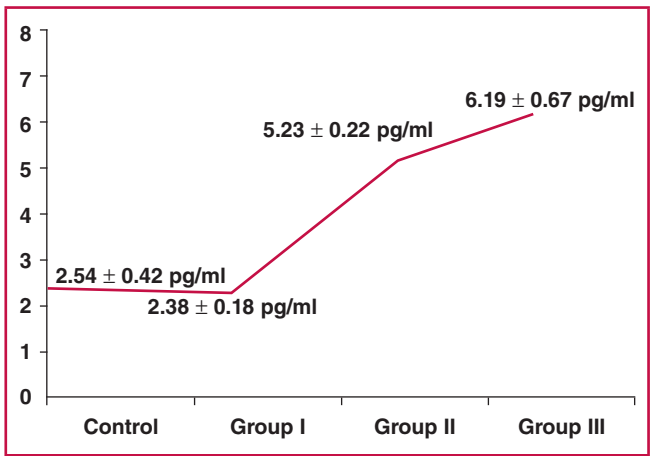

Fig. 1. CNP levels according to duration of induced mesenteric ischaemia.

factor-1 (TGF-1)-induced collagen production in cultured fibroblasts.[14] Recent reports have suggested that CNP has cardio–renal protective effects via these humoral mechanisms in the setting of stress injury, with suppression of pro-fibrotic processes and a protective function.[14-16]

Furthermore, CNP has local regulatory functions via the vascular renin–angiotensin system. CNP inhibits the vasoconstrictor impact of angiotensin 1. Additionally, recent reports suggest that CNP is an endogenous regulator of vascular ACE activity. Higher CNP levels were demonstrated both in renal failure patients who were on haemodialysis therapy and in cardiac failure patients.[15,16]

In a recent study it was reported that CNP lacked renal action but led to vasodilatation and inhibition of growth.[19] These data indicate that CNP is a non-cardiac regulator hormone that regulates vascular tone according to cardio–renal interactions via different mechanisms, such as the vascular renin–angiotensin system.[15-17]

Natriuretic peptides are potent vasodilators during hypoxic conditions. For example, Klinger *et al.* reported pulmonary vessel vasodilation in response to natriuretic peptides in rats adapted to hypoxic environments.[9] Similarly, Zhao *et al.* described the possible use of natriuretic peptides in maintaining pulmonary vascular homeostasis in hypoxic patients.[18]

Hobbs *et al.* studied CNP in an experimental model of myocardial ischaemia–reperfusion and found that CNP had protective vasorelaxation properties.[19] Ahluwalia *et al.* demonstrated that hypoxia might directly induce the release of CNP so that vascular homeostasis is maintained.[20]

It has been reported that CNP may contribute to the regulation of blood flow with decreasing perfusion pressure and also reduce the oxidative damage after reperfusion in ischaemic conditions.[19] Additionally, it was hypothesised that CNP was upregulated in the presence of nitric oxide (NO) synthase inhibition for compensation of the protective role of NO.[19]

In another study, it was shown that CNP led to an increment in NO stimulation and suppression of the neo-intimal hyperplasia and inflammatory process in an experimental carotid injury model.[21] Chun *et al*. demonstrated that oxidative stress could modulate the endothelium-derived vasoactive substances such as CNP.[22] Yamahara *et al*. claimed that CNP enhanced angiogenesis in ischaemic conditions in their experimental model.[23] All these studies identified a range of cellular and vascular interactions that may clarify the role of elevated CNP levels due to oxidative stress during mesenteric ischaemia after reperfusion.

Conclusion

CNP appears to regulate blood flow in the mesenteric vascular bed. Clinically monitoring CNP levels may be useful in estimating the duration over which the patient has sustained mesenteric ischaemia and the severity of the injury due to acute mesenteric artery occlusion. However, the exact mechanism of the interaction between CNP and the mesenteric vessels must be further elucidated in future clinical studies.

We thank the co-ordinator of scientific research at Dicle University for language-editing the manuscript.

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Cardiac surgery for patients with heart failure due to structural heart disease in Uganda: access to surgery and outcomes

Antonio Grimaldi, Enrico Ammirati, Nicole Karam, Anna Chiara Vermi, Annalisa De Concilio, Giorgio Trucco, Francesco Aloi, Francesco Arioli, Filippo Figini, Santo Ferrarello, Francesco Maria Sacco, Renato Grottola, Paul G D'Arbela, Ottavio Alfieri, Eloi Marijon, Juergen Freers, Mariana Mirabel

Abstract

Objective: Few data are available on heart failure (HF) in sub-Saharan Africa. We aimed to provide a current picture of HF aetiologies in urban Uganda, access to heart surgery, and outcomes.

Methods: We prospectively collected clinical and echocardiographic data from 272 consecutive patients referred for suspected heart disease to a tertiary hospital in Kampala during seven non-governmental organisation (NGO) missions from 2009 to 2013. We focused the analysis on 140 patients who fulfilled standardised criteria of HF by echocardiography.

Results: Rheumatic heart disease (RHD) was the leading cause of HF in 44 (31%) patients. Among the 50 children included (age ≤ 16 years), congenital heart disease (CHD) was the first cause of HF (30 patients, 60%), followed by RHD (16 patients, 32%). RHD was the main cause of HF (30%) among the 90 adults. All 85 patients with RHD and CHD presented with an indication for heart surgery, of which 74 patients were deemed fit for intervention. Surgery was scheduled in 38 patients with RHD [86%, median age 19 years (IQR: 12–31)] and in 36 patients with CHD [88%, median age 4 years (IQR 1–5)]. Twenty-seven candidates (32%) were operated on after a median waiting time of 10 months (IQR 6–21). Sixteen (19%) had died after a median of 38 months (IQR 5–52); 19 (22%) were lost to follow up.

Conclusions: RHD still represents the leading cause of HF in Uganda, in spite of cost-efficient prevention strategies. The majority of surgical candidates, albeit young, do not have access to treatment and present high mortality rates.

Keywords: heart failure, rheumatic heart disease, congenital heart disease, echocardiography, heart surgery

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Improvement in the control of infectious diseases and malnutrition associated with changes in lifestyle has led to a new epidemiological pattern in many low- and middle-income countries. Non-communicable diseases, mainly cardiovascular disorders, have emerged as major causes of morbidity and mortality in most sub-Saharan African countries.[1] Hospital-based studies indicate that heart failure (HF) accounts for 3–7% of all admissions to African hospitals.[2,3-7]

Although there has been increasing interest in the epidemiology of cardiovascular diseases in the African continent,[7-9] recent data from Uganda are scarce[7,10] but most needed to guide public health policies. Most registers originate from South Africa and cannot be transposed to poorer sub-Saharan countries.[2,11]

Echocardiography is a mainstay in the assessment of HF. Unfortunately, access to echocardiography remains limited in many African countries due to cost and lack of skilled health workers, thereby leading to little data on cardiovascular diseases.[12]

We report on the distinctive patterns of HF through a prospective, cross-sectional, hospital-based study in patients referred for suspected heart disease in urban Kampala, Uganda,

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in order to characterise the features of HF and to tailor future interventions. We also aimed at assessing access to invasive interventions and outcomes in patients with surgical indications.

Methods

Study setting

The study was conducted at the St Raphael of St Francis Nsambya Hospital, a tertiary, non-profit hospital with a capacity of 361 beds, located in urban Kampala. Uganda has a population of 33 425 000 and a life expectancy of 48 and 57 years in males and females, respectively (http://www.who.int/countries/uga/en/)]. The Italian association Solidarity Among People (AISPO), a non-governmental organisation (NGO) managed by the San Raffaele Scientific Institute in Milan, Italy, conducted the project in co-operation with local medical staff.

The main objectives of the project were to gather epidemiological data on HF in Uganda, and to train Ugandan doctors, with a special focus on echocardiographic skills. The present study was conducted during seven NGO missions (cumulative period of 36 weeks from 2009 to 2013). The seventh mission was performed in 2013 in order to follow up on patients who had undergone surgery and those still on the waiting list. Patients were systematically evaluated by clinical and echocardiographic examination.

Study cohort

We prospectively studied 272 consecutive subjects [median age 35 years, interquartile range (IQR) 17–58; 59% female] referred to the St Raphael of St Francis Nsambya Hospital for suspected heart disease. Patients were evaluated by clinical and echocardiographic examination. Electrocardiogram, chest X-ray, chest computerised tomography (CT) scan and venous Doppler examination of the inferior limbs were performed as needed.

We studied 160 out-patients (59%) and 112 in-patients (41%) from the general medical and paediatric wards. In the study population, 149 patients (55%) were female and 75 (27%) were children (≤ 16 years). Shortness of breath was the most frequent motive for seeking medical assistance (n = 114, 42%). One hundred and ninety-seven patients (72%) presented with structural heart disease, among which 140 (71%) were in clinical HF.[13] The latter constituted the study cohort (Fig. 1).

Echocardiographic evaluation and study definitions

Italian cardiology teams from the San Raffaele Scientific Institute in Milan carried out the echocardiograms. General Electric® Logic P5 machines with colour Doppler and two available probes (1.5–3.5 MHz for adults and 3–8 MHz for children) were used. Two experienced cardiologists reviewed all echocardiograms for definite diagnosis (AG and EA).

The aetiology of HF was assessed according to the European Society of Cardiology guidelines.[13] HF was defined as systolic HF when left ventricular ejection fraction (LVEF) was < 50%; preserved ejection fraction HF when signs of increased left ventricular filling were detected; and right ventricular HF when the right ventricle was primarily affected or dysfunctional due to pulmonary hypertension (PH) not associated with left-sided heart abnormalities.

Ischaemic heart disease (IHD) was suspected when clear wall motion abnormalities were observed (there was no cardiac

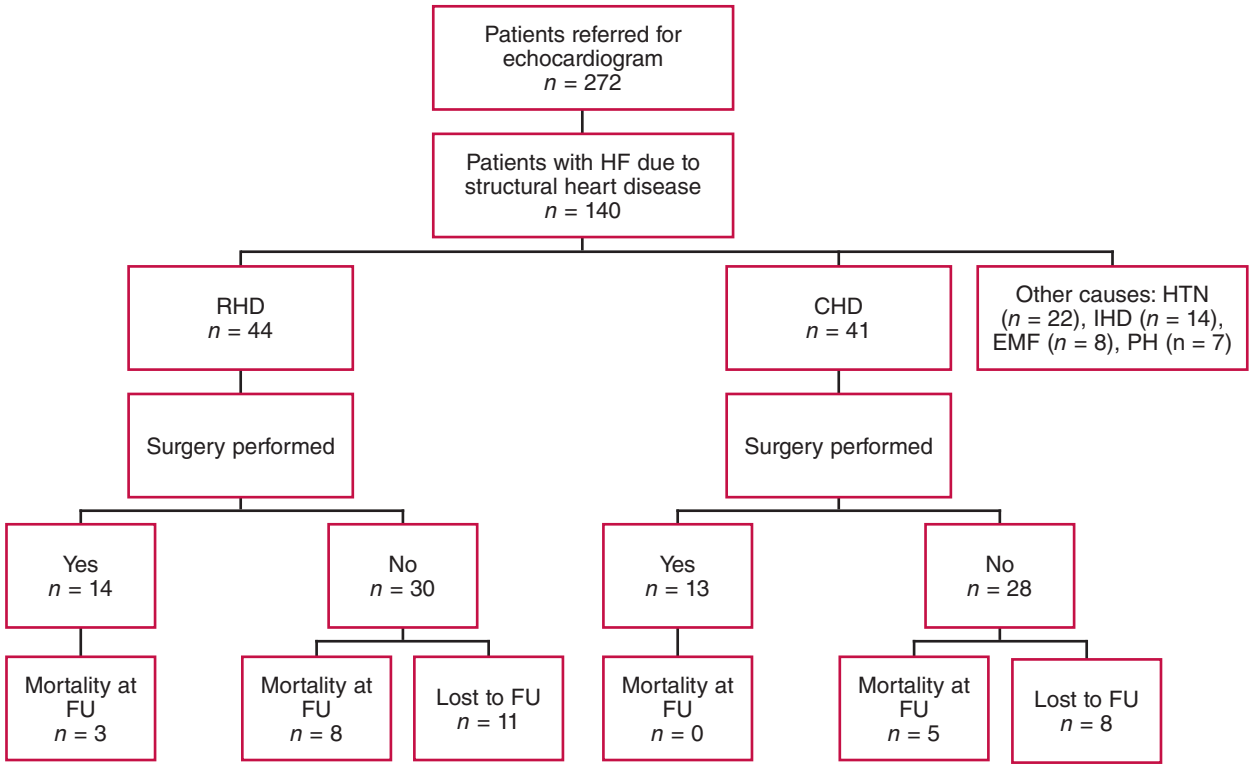

Fig. 1. Flow chart and surgical treatment in patients with rheumatic and congenital heart disease. FU = follow up

catheterisation laboratory in Uganda at the time of the study). HF was defined as hypertensive when long-lasting history of systemic hypertension and typical echocardiographic features such as left ventricular concentric hypertrophy or impaired left ventricular inflow patterns were found. We identified patients as potential candidates for cardiac surgery according to the current guidelines.[14]

This study was approved by the St Raphael of St Francis Nsambya Hospital Ethical Committee (May 2009). It conformed to the Declaration of Helsinki and Good Clinical Practice.

Statistical analysis

We performed descriptive statistics for the more frequently observed heart diseases. The results are reported as median and interquartile range, or as numbers and percentages, as appropriate.

Results

Causes of HF in the whole cohort and according to age

The study group constituted a cohort of 140 patients with clinical HF. Median age was 40 years (IQR 14–66) and 83 (59%) were female. All patients were black Africans. The predominant cause of HF was RHD (n = 44; 31%) (Fig. 2A), mainly related to severe mitral regurgitation, which was either isolated or associated with multiple valve involvement. Other main causes of HF were CHD (n = 41; 29%), hypertensive cardiomyopathy (n = 22; 16%), highly suspected IHD (n = 14; 10%), endomyocardial fibrosis (EMF) (n = 8; 6%) and right ventricular failure due to pre-capillary PH (n = 7; 5%).

LVEF was reduced in 56 cases (40%). Moderate to severe right ventricular dysfunction was found in 70 (50%) cases. Clinical and echocardiographic characteristics of patients with HF are depicted in Table 1.

We further analysed causes of HF separately in children and adults (Fig. 2B, C). In the paediatric population [n = 50, age ≤ 16 years, median 6 (IQR 2–12)] CHD was the main cause of HF (n = 30; 60%), followed by RHD (n = 16; 32%). We also reported three cases of EMF (6%). In the first decade of life, CHD was the main cause of HF (29/31, 97%), while RHD was the most prevalent in the age group of 10 to 16 years (15/17, 94%).

In adults [n = 90, age > 16 years; median 55 (IQR 33–70)], RHD was the primary cause of HF (n = 27; 30%). Hypertensive cardiomyopathy and presumptive IHD were the most frequent causes of HF beyond the sixth decade of life. Overall, hypertensive cardiomyopathy and IHD ranged as second and third causes of HF in adults, 24 and 15%, respectively. Other causes are depicted in Fig. 2C.

Rheumatic heart disease

RHD (n = 44) was the main cause of HF in adults and the second in children. Table 1 shows the echocardiographic features of RHD. The median age of patients with RHD complicated by HF was 19 years (12–52) with a female:male ratio of 2.1:1.

Briefly, the mitral valve was affected in all cases. Mitral regurgitation was the most common lesion (43/44 cases, 98%) and the degree of mitral regurgitation was often severe (29/43, 67%). Mitral stenosis was severe in 12 patients (27%). PH (i.e. pulmonary artery systolic pressures > 35 mmHg) was present in 43 subjects [98%; median 65 (50–70 mmHg)]. Moderate and severe right ventricular dysfunction was present in 27 patients (61%). Moderate to severe tricuspid regurgitation was present in 36 patients (82%) due to annular dilatation secondary to RV remodelling without significant rheumatic involvement.

Representative images of mitral lesions implicated in HF are shown in Fig. 3. We observed three main patterns of rheumatic mitral regurgitation: (1) symmetrical restriction of leaflets (30 cases, Fig. 3A); (2) posterior leaflet restriction and anterior leaflet pseudo-prolapse (eight cases, Fig. 3B); and (3) leaflet restriction and chordal rupture (five cases; Fig. 3C). Mitral lesions that did not appear calcified that were deemed suitable for surgical repair.

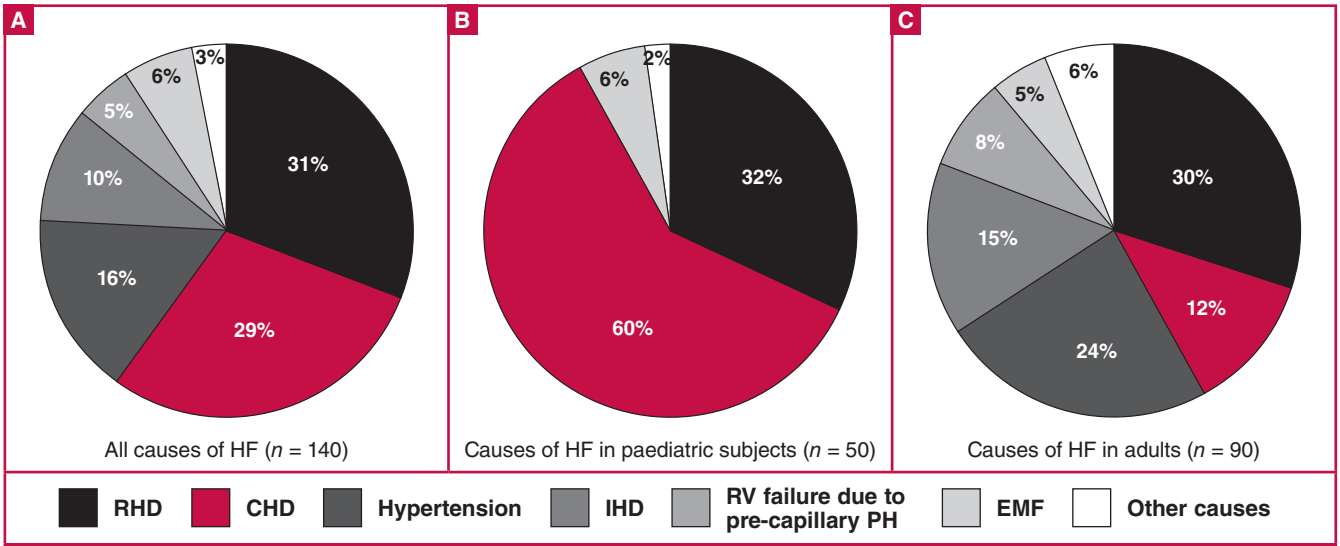

Fig. 2. Main causes of heart failure (HF) in the study population (A), in paediatric subjects (B), and in adults (C). RHD = rheumatic heart failure, CHD = congenital heart disease, IHD = ischaemic heart disease, RV = right ventricular, PH = pulmonary hypertension, EMF = endomyocardial fibrosis.

Table 1. Clinical and echocardiographic characteristic of 113 patients with heart failure.

Main cause of HF	*RHD*	*CHD*	*Hypertensive CMP*	*IHD*	*EMF*	*RVD associated with PH*	*Miscellaneous*	*Total*
No of cases (%)	44 (31)	41 (29)	22 (16)	14 (10)	8 (6)	7(5)	4 (3)	140
Age (years) [median (IQR)]	19 (12–52)	4 (1–17)	66 (56–76)	75 (60–85)	18 (14–30)	50 (38–72)	50 (32–66)	40 (14–66)
Females, *n* (%)	36 (82)	21 (58)	13 (59)	5 (36)	3 (37)	3 (43)	2 (50)	83 (59)
LV systolic dysfunction, *n* (%)	13 (29)	7 (17)	16 (73)	13 (93)	2 (25)	2 (28)	4 (100)	57 (41)
LVEF % [median (IQR)]	60 (40–60)	60 (57–60)	37 (20–55)	35 (25–40)	55 (45–60)	55 (48–58)	40 (30–40)	55 (35–60)
LV dilatation*, *n* (%)	30 (68)	10 (24)	12 (54)	8 (57)	1 (12)	0 (0)	3 (75)	64 (46)
LA severe dilatation§, *n* (%)	38 (86)	5 (12)	10 (45)	1 (7)	2 (25)	0 (0)	1 (25)	57 (41)
AF, *n* (%)	5 (11)	0 (0)	8 (36)	1 (7)	0 (0)	0 (0)	0 (0)	14 (10)
Moderate to severe MR, *n* (%)	39 (89)	10 (24)	12 (54)	5 (36)	6 (75)	2 (28)	2 (50)	76 (54)
PH, *n* (%)	43 (98)	34 (81)	20 (91)	7 (50)	7 (87)	7 (100)	2 (50)	120 (86)
Moderate to severe RV dysfunction, *n* (%)	27 (61)	20 (49)	12 (54)	3 (21)	8 (100)	6 (86)	1 (25)	77 (55)

RHD = rheumatic heart disease, CHD = congenital heart disease, CMP = cardiomyopathy, IHD = ischaemic heart disease, RVD = right ventricular dysfunction, PH = pulmonary hypertension, EMF = endomyocardial fibrosis, LV = left ventricle, EF = ejection fraction, LA = left atrium, AF = atrial fibrillation, MR= mitral regurgitation, RV= right ventricle.
*Defined as end-diastolic diameter > 55 mm for adults.
§Defined as volume > 40 ml for adults, PH defined as pulmonary artery systolic pressure > 35 mmHg.

Congenital heart disease

CHD (n = 41) was the main cause of HF in children under 16 years (30/50; 60%). Table 2 summarises the type of congenital defects observed. The main diseases associated with HF in children were isolated ventricular septal defect (VSD) (n = 7/30, 23%), atrio-ventricular septal defects (AVSD) (n = 4/30, 13%) and tetralogy of Fallot (n = 4/30, 13%). Other abnormalities included isolated atrial septal defects (ASD) (n = 6/41, 15%) and persistent ductus arteriosus (PDA) (n = 5/41, 12%).

Complex congenital defects were observed in 11 children (11/30, 37%), including rare diseases such as type II persistent truncus arteriosus and aortopulmonary window. Uncorrected CHD was responsible for HF in 11 adults (11/90; 12%), including two cases (5%) of Eisenmenger syndrome and two cases (5%) of severe Ebstein anomaly.

Other aetiologies of structural heart disease

We reported eight cases of EMF in HF (6% of all causes of HF in our series). The echocardiographic findings of biventricular EMF were similar in all cases, with the exception of the degree of right ventricular obstruction. In two cases, there was a significant obliteration of the right inflow tract and the apex (Fig. 4A). In the other case, the fibrosis involved only the right apex (Fig. 4B). We also observed a rare case of calcified isolated LV EMF (Fig. 4C).

The proportion of patients with HF associated with hypertension (n = 22/140; 16%) or presumptive IHD (n = 14/140; 10%) increased in older patients, with a peak incidence (33/52 among the 90 adults) in the seventh decade (Table 1). Pulmonary hypertension and right HF not associated with left-sided heart abnormalities accounted for 5% (7/140 cases) of causes of HF. Pulmonary embolism (6/7 cases, 86%) was recognised as the main cause of PH associated with right-sided HF. In four cases, CT scans or venous Doppler examination of the inferior limbs also supported the diagnosis.

Patients with an indication for cardiac surgery: access to treatment, and outcomes

Among 85 patients with HF related to RHD and CHD, all presented a theoretical indication for cardiac surgery, and 74

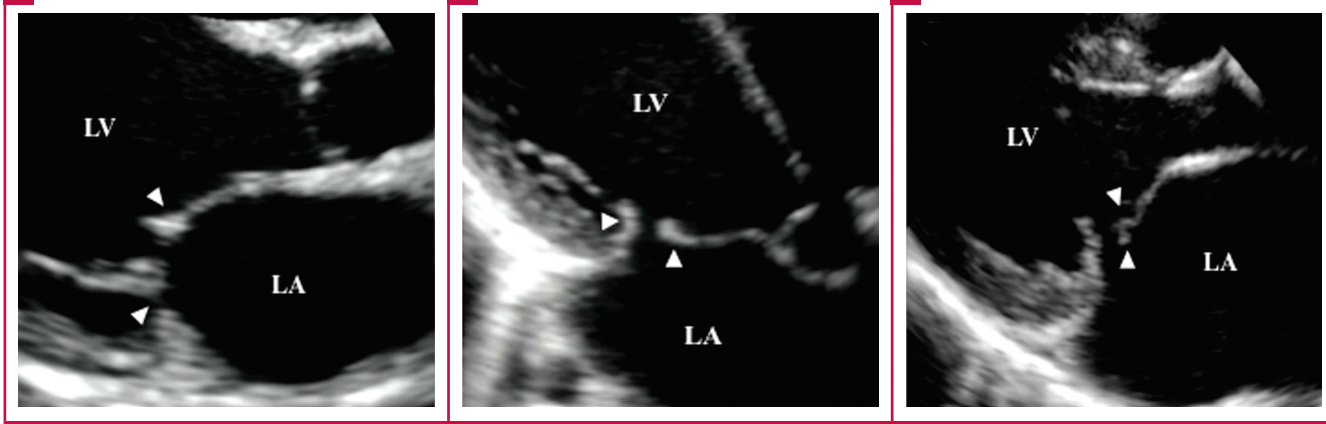

Fig. 3. Three main patterns of rheumatic mitral regurgitation (MR). (A) Symmetrical restriction of leaflets and annular dilatation. (B) Restricted posterior leaflet and pseudo-prolapse of the anterior leaflet. (C) Restricted posterior leaflet and ruptured chordae tendineae of the anterior leaflet. LV = left ventricle, LA = left atrium.

Table 2. Types of congenital heart defects causing heart failure in the paediatric and adult populations.

Type of defect, n *(%)*	*≤ 16-year-old* n = *30 (73)*	*>16-year-old* n = *11 (27)*	*Total* n = *41 (29)*
Simple defects	19 (63)	8 (73)	27 (66)
Atrial septal defect	3 (10)	3 (27)	6 (15)
Ventricular septal defect (VSD)	7 (23)	0 (0)	7 (17)
Atrio-ventricular septal defect	4 (13)	0 (0)	4 (10)
Congenital mitral cleft	1 (3)	0 (0)	1 (2)
Persistent ductus arteriosus	3 (10)	2 (18)	5 (12)
Congenital aortic regurgitation	0 (0)	1 (9)	1 (2)
RV outflow tract obstruction	1 (3)	2 (18)	3 (7)
Complex defects	11 (37)	3 (27)	14 (34)
Tetralogy of Fallot	4 (13)	1 (9)	5 (12)
VSD + pulmonary stenosis	1 (3)	0	1 (2)
VSD + tricuspid dysplasia	1 (3)	0	1 (2)
Univentricular heart	2 (7)	0	2 (5)
Persistent truncus arteriosus	2 (7)	0	2 (5)
Aorto-pulmonary window	1 (3)	0	1 (2)
Ebstein anomaly	0	2 (18)	2 (5)
Eisenmenger syndrome	0	2 (18)	2 (5)

were deemed fit for surgery. Intervention was scheduled in 38 patients with RHD (86%) [median 19 years (IQR 12–31)] and in 36 patients (88 %) with CHD [median 4 years (IQR 1–5)]. Eleven patients (13%) presented with co-morbidities or at an advanced stage and were not considered surgical candidates. Data concerning major outcomes and surgical follow up are depicted in Fig. 1.

Twenty-seven patients (14 with RHD and 13 with CHD) were operated on during the study period, accounting for 36% (27/74) of patients deemed suitable for surgery. Selection was based on expected benefit from the surgery, with the most favourable risk:benefit ratio, familial support and patients' consent. Despite the low surgical risk, two patients suffering from Down syndrome were not considered suitable for heart surgery due to the expected survival rate in deprived areas. Surgery was performed after a median waiting time of 10 months (IQR 6–21) in foreign hospitals funded by NGOs.

Among 14 patients with RHD, 13 (93%) underwent mitral surgery, both replacement ($n = 10$, 77%) and repair surgery ($n = 3$, 23%) such as annuloplasty, implantation of artificial cordae and commissurotomy. Combined mitral and aortic valve replacement was performed in two patients (14%). Tricuspid repair surgery was performed in four patients (28%).

Among 13 patients with CHD, surgical treatment included four cases (31%) of VSD closure, two (15%) of AVSD repair, two (15%) of PDA ligation and one case (8%) of ASD. closure. Four patients (31%) underwent surgery for complex congenital defects (two with tetralogy of Fallot, one with aortopulomonary window, one with persistent truncus arteriosus).

Among 85 patients with HF related to RHD and CHD, 16 (19%) had died by follow up after a median of 38 months (IQR 5–52), and 19 (22%) were lost to follow up (Fig. 1). There were 13 deaths (15%) among patients who did not undergo surgery despite the presence of clear indications, one peri-operative death and two late post-operative deaths due to complications related to mechanical valves (one endocarditis, and one severe brain haemorrhage).

Nineteen patients (22%) were lost to follow up and were considered as not operated, given the lack of access to cardiac surgery in Uganda. Twelve out of the 19 patients lost to follow up were likely to have died due to to advanced disease at the time of diagnosis. All patients who had undergone cardiac surgery experienced improvement in clinical symptoms (22 patients reverting to NYHA class I; two patients reverting to NYHA class II).

Discussion

We report here the first prospective hospital-based series of HF patients in Uganda and show that RHD, a preventable disease, remains the major cause of HF in a young population. However, CHD was the leading cause among children, especially those under 10 years. Other causes were also identified as hypertensive cardiomyopathy, endomyocardial fibrosis and presumed ischaemic heart disease. A small fraction of young surgical candidates had access to treatment through the efforts of NGOs. We believe our study will add to the knowledge of cardiovascular

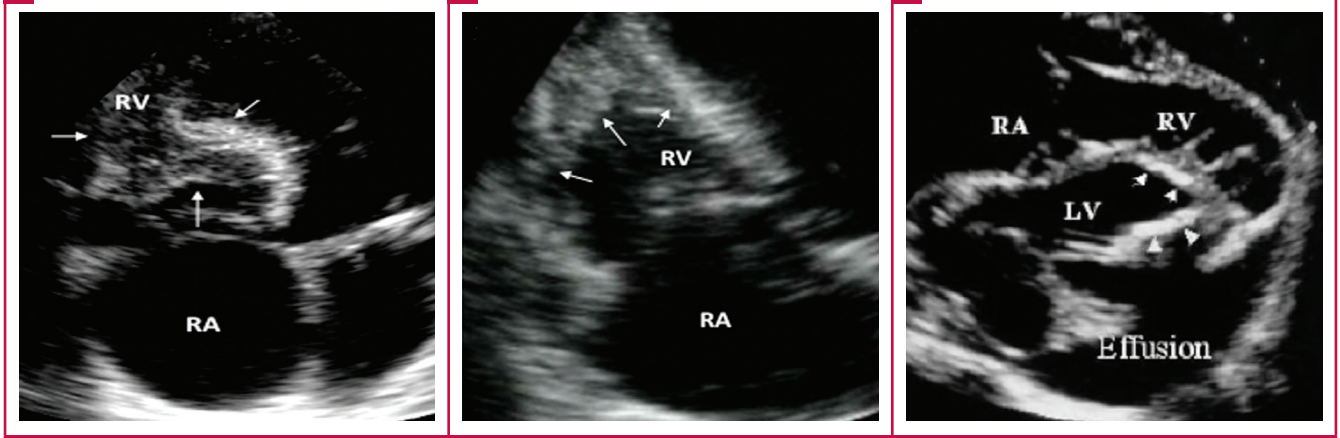

Fig. 4. Three main patterns of endomyocardial fibrosis (EMF). (A) Fibrotic obliteration of the right ventricular inflow cavity. (B) Limited fibrotic involvement of the right apex. (C) A rare case of calcified isolated LV EMF. RV = right ventricle, RA = right atrium, LV = left ventricle.

disease in sub-Saharan Africa, as robust echo-based data are limited,[5,15-17] and surgical outcomes seldom depicted.

Regarding the aetiology of HF, our findings are consistent with those of other sub-Saharan countries, as illustrated in Table 3.[4,5,7,15-17] In Uganda, RHD remains the leading cause of HF in young adults and the second cause in children. As in other series, we found that RHD affected mostly young women in the third decade of life, and that mitral regurgitation was the most common presentation.[18] Diagnosis was often made when left ventricular function was already impaired, requiring intervention.

Our study underscores the need for preventive strategies in order to lessen the burden of RHD in Africa. RHD is a preventable disease provided patients receive penicillin for Group A streptococcal pharyngitis (primary prevention) or after a first attack of acute rheumatic fever (secondary prevention). Notwithstanding, RHD remains a major burden in low-income countries, affecting 15 million people and leading to at least 200 000 deaths per annum worldwide.[19,20]

Diagnosis is often made when costly interventions are required, leaving most sub-Saharan African patients to the natural course of the disease. Comprehensive programmes focusing on secondary prophylaxis are cost-efficient and could avoid progression to irreversible valve damage. Our study advocates launching preventive strategies in Uganda. The role of echocardiography-based screening in endemic areas is still a matter of controversy.[21-24]

In our study, CHD was the main cause of HF among children and accounted for up to 9% of HF among adults, suggesting the need for diagnostic expertise in echocardiography and for cardiac surgery facilities.[9] While in developed countries prenatal diagnosis is currently used to detect CHD, access to diagnosis and treatment are limited in low-income countries.[25] Furthermore, simple CHD may be cured by timely surgical or percutaneous treatment, whereas a delayed diagnosis increases morbidity and mortality rates. Efforts should focus on early detection of CHD and on building a referral system for diagnosis, management and follow up of patients in a resource-deprived setting.[25]

In contrast with previous reports,[3,26] endomyocardial fibrosis in the urban area of Kampala no longer seems to be the main cause of HF. That could be ascribed to improved socio-economic conditions. It must be stressed that the nationwide prevalence of the disease could be higher, as suggested by an echocardiography-based screening study performed in rural Mozambique.[27] Urban Uganda seems to follow the trend of the epidemiological transition witnessed in many African countries, with the emergence of hypertensive cardiomyopathy and IHD as major causes of HF in adults.[4,7,16]

The progression to hypertensive cardiomyopathy could be halted through early diagnosis and appropriate treatment, including the reduction of salt intake. Raising awareness among the general population and health workers should therefore become a priority in African countries,[28] and could be achieved by training primary healthcare practitioners to use simple algorithms to score cardiovascular risk and initiate treatment when needed.

We found that right ventricular failure due to PH was relatively common in adults, in agreement with the results from other African studies.[4,5,7,16-18] Unlike a recent multinational survey including nine countries, we did not diagnose patients with post-tuberculosis or HIV-related cardiomyopathy, and we found only one case of post-partum cardiomyopathy.[7] We encountered no cases of cor pulmonale due to post-tuberculosis lung damage, tuberculosis-related pericarditis or HIV-related cardiomyopathy in spite of HIV being endemic in Uganda (http://www.unaids.org/en/dataanalysis/knowyourepidemic/epidemiologicalfactsheets/).

Although the epidemiology of cardiovascular diseases is usually treated in African countries as a whole,[8] differences in climate, diet and income may explain apparent discrepancies between regions. The fact that our study was conducted in an urban area may also account for these conflicting results.

As outlined by our series in which only 36% of surgical candidates had access to treatment and 18% died on the waiting list, there is an urgent need for comprehensive service frameworks to improve level of care, and services by NGOs are insufficient to treat all patients in need of treatment. With the exception of South Africa, access to cardiac expertise and heart surgery remains extremely limited in most sub-Saharan countries.[9] The absence of trained physicians is a barrier to tackling the burden of cardiovascular disease, a growing public health issue in Africa.[29]

Table 3. Echo-based diagnosis of heart failure in sub-Saharan Africa.

	Uganda	*Nigeria*[16]	*South Africa*[5]	*Ghana*[4]	*Malawi*[17]*	*Cameroon*[15]	*THESUS-HF*[7§]
Inclusion period	2009–2013	2002–2006	2006	1992–1995	2001–2005	2002–2008	2007–2010
Settings	Kampala	Abuja	Soweto	Accra	Mzuzu	Kumbo	9 nations
Total sample size	272	–	1960			8121	
Population with CVD	190	–			3908*		
Sample size with HF	140	340	844 (de novo)	572	–	462	1006
Age	40 (14–66)	51 ± 15	55 ± 16	42 ± 1	40 ± 32	43 ± 18	52 ± 18
Females, *n* (%)	59	49	57	45	59	43	51
Causes of HF							
First aetiology	RHD	HCMP	HCMP	HCMP	RHD	RHD	HCMP
Second aetiology	CHD	DCMP	DCMP	RHD	HCMP	DCMP	DCMP
Third aetiology	HCMP	RHD	Right HF	DCMP	DCMP	HCMP	RHD

CVD = cardiovascular disease, HF = heart failure, RHD = rheumatic heart disease, HCMP = hypertensive cardiomyopathy, DCMP = dilated cardiomyopathy.
*Data from these studies are presented as mean ± SD or median (IQR) as available. In the study by EZ Soliman, the registry did not specifically address the causes of HF, but the main causes of cardiovascular disease.
§THESUS-HF = THE SUb-Saharan Africa survey of Heart Failure was a prospective survey of patients with acute HF admitted to 12 university hospitals in nine sub-Saharan countries: South Africa, Mozambique, Uganda (*n* = 154), Kenya, Ethiopia, Sudan, Senegal, Nigeria and Cameroon.

Efforts to overcome these hurdles have resulted in two types of humanitarian projects: the creation of well-equipped, on-site healthcare structures, and the transfer of patients, mainly children, with complex diseases to receive highly specialised care abroad. Our programme was based on providing surgery in European centres. However, prospective studies with long-term follow up to clearly define whether these strategies are effective in reducing infant and young adult mortality in the sub-Saharan socio-economic background are warranted.

Strengths and limitations

The study was conducted by skilled cardiologists who are experienced in the assessment of valvular heart disease, in collaboration with local medical staff who were previously involved in other studies on the causes of HF in Uganda.[3,12] The diagnosis was therefore robust. The prospective nature of the study has enabled us to form a cohort of patients with structural heart disease and to organise follow up. We provide here original and scarce data on the selection and outcomes of heart surgery candidates in a poorly resourced country.

Our results appear to be in agreement with previous data from other sub-Saharan hospital-based registries, with the exception of tuberculosis and HIV-related heart disorders. Our study was based on a prospectively collected patient cohort from a tertiary teaching hospital, which does not allow us to draw conclusions on the prevalence of HF and its associated echocardiographic patterns in the general population. IHD diagnosis was only presumptive because at the time of the study coronary angiography was not available in Uganda.

Finally, the sample size was relatively modest due to the limited time period of the NGO missions and we acknowledge high rates of loss to follow up. Also, we decided not to analyse outcomes according to treatment in RHD and CHD patients, due to methodological constraints (high rate of lost to follow up in a country with no nationwide mortality register, survivor treatment selection bias). Although descriptive, our study complies with the STROBE guidelines.[30] We attempted to contact every patient, however, remoteness, frequent changes of mobile phones, and cultural boundaries may explain the difficulties in contacting all patients or their next of kin.

Conclusions

Rheumatic heart disease prevails as the leading cause of heart failure in urban Uganda, and CHD represents an increasing challenge for African practitioners, whereas hypertensive and ischaemic heart disease emerge among elderly adults. Only a minority of young surgical candidates with RHD and CHD have access to treatment. Mortality rate remains high. Cost-effective preventive strategies for RHD and hypertension, rational referral services for early diagnosis, and north–south transfer of skills may lessen the growing burden of cardiovascular diseases in Africa.

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Diabetes researchers track cells' ability to regenerate

Vanderbilt University scientists have found evidence that the insulin-secreting beta-cells of the pancreas, which are either killed or become dysfunctional in the two main forms of diabetes, have the capacity to regenerate. The surprising finding, posted online by *Cell Metabolism* earlier this year, suggests that by understanding how regeneration occurs, scientists may one day be able to stop or reverse the rising tide of diabetes. 'The study provides clues to how we might learn what signals promote beta-cell regeneration in type 1 and type 2 diabetes', said Dr Alvin Powers, the senior author and director of the Vanderbilt Diabetes Center.

In the past three months, the Powers group at Vanderbilt, in four separate articles, has reported important findings about the 'microenvironment' of the insulin-secreting beta-cells and glucagon-secreting alpha-cells, which are among four types of cells clustered in islets in the pancreas. Both hormones are important in regulating blood glucose levels and ensuring that glucose is delivered to the muscles and brain to be used as fuel, and stored in the liver. Powers called the islets a 'mini-organ' because they are highly vascularised and innervated, and exist within a specialised environment.

In type 1 diabetes, the beta-cells are destroyed and glucose levels rise in the blood because not enough insulin is being produced. In type 2 diabetes, a frequent consequence of obesity, tissues become resistant to insulin, again causing blood glucose to rise. Beta-cell function also becomes abnormal.

In two articles in the journal *Diabetes* and one each in *Development* and *Cell Metabolism*, the researchers described four main findings about islet vascularisation and innervation. First, vascular endothelial growth factor A (VEGF-A) is important for development of the islets' blood supply and for beta-cell proliferation. Blocking the growth factor early in development in a mouse model ultimately reduced beta-cell mass and insulin release and impaired glucose clearance from the bloodstream.

Second, VEGF and other 'signals' released by the endothelial cells lining the islet blood vessels consequently stimulated growth of islet nerves in mice that connected to the brain. 'If the islets don't become vascularised properly, they don't become innervated properly', Dr Marcela Brissova, who was co-author on three of the four articles, said. 'These signals also promote beta-cell growth.'

Third, VEGF-A was not involved when the beta-cell mass increased in an obese mouse model of type 2 diabetes in response to rising glucose levels. Unlike tumours, which sprout new blood vessels as they grow, the beta-cell tissue increased its blood supply by dilating existing vessels.

Finally, too much VEGF-A can lead to beta-cell death. But that sets up a regenerative micro-environment involving an interaction of vascular endothelial cells and macrophages, which, in turn, leads to beta-cell proliferation both in mice and human islets. 'That's very unusual because islet cells are like neurons; once they're dead, they don't usually regrow', Brissova said. 'We think that the endothelial cells and macrophages that are recruited from bone marrow create an environment that promotes the proliferation and regeneration of those beta-cells.'

Source

http://medicalxpress.com/news/2014-03-diabetes-track-cells-ability-regenerate.html

Effects of rosuvastatin on ADMA, rhokinase, NADPH oxidase, caveolin-1, hsp 90 and NFkB levels in a rat model of myocardial ischaemia–reperfusion

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Abstract

Aim: Endothelial dysfunction, oxidative stress and inflammation are among the most important mechanisms of ischaemia–reperfusion (I/R) injury. Besides their cholesterol-lowering effects, statins are known to provide protection against myocardial dysfunction and vascular endothelial injury via nitric oxide-dependent mechanisms. The aim of this study was to investigate the effects of rosuvastatin on certain intermediates involved in the generation of nitric oxide (asymmetrical dimethyl arginin, ADMA, caveolin-1 and hsp 90), oxidative stress (rhokinase, NADPH oxidase) and inflammation (NFkB), using an *in vivo* model of myocardial infarction in the rat.

Methods: Adult male Sprague Dawley rats were divided into three groups (control, I/R and I/R after 15 days of rosuvastatin administration). Reperfusion was applied for 120 min following left anterior descending coronary artery ischaemia for 30 min. Caveolin-1, hsp 90 and NFkB levels were evaluated with the quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) and ADMA, rhokinase and NADPH oxidase levels were evaluated with ELISA.

Results: While NFkB and hsp 90 levels were higher in the I/R group, their levels were significantly lower in the rosuvastatin group. While ADMA and NADPH oxidase levels significantly increased with I/R, they were lower in the rosuvastatin-treated group, but not statistically significant. Rhokinase levels were significantly lower in the rosuvastatin group. Caveolin-1 levels were not different between the groups.

Conclusion: Our results suggest that ADMA, rhokinase, NADPH oxidase, hsp 90 and NFkB could facilitate I/R injury, and rosuvastatin significantly reduced levels of these parameters. These results indicate that rosuvastatin may have a protective role in I/R injury via mechanisms targeting inflammation, endothelial dysfunction and oxidative stress.

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Keywords: ischaemia–reperfusion, rosuvastatin, oxidative stress, ADMA, hsp 90, caveolin-1, NFkB, rhokinase, NADPH oxidase

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Ischaemic heart disease remains among the major causes of morbidity and mortality worldwide. The most common form is reduction in blood flow in the coronary arteries supplying blood to the myocardium due to atherosclerotic plaques or vasospasm.[1] After ischaemia, reperfusion of the tissue is of great importance for maintenance of the viability of the ischaemic tissue. However reperfusion may paradoxically lead to some morphological changes, enzyme destruction and even death of the still-viable tissue that may be rescued.[2]

Ischaemia–reperfusion (I/R) injury is the mainstay of myocardial infarction, cerebral ischaemia, stroke, haemorrhagic shock and surgical interventions such as organ transplantation, cardiac surgery, coronary angioplasty and thrombolytic treatment-related pathophysiology.[3] Endothelial dysfunction, oxidative stress and inflammation are among the most common mechanisms of I/R injury.[4,5]

Asymmetrical dimethyl arginine (ADMA) is an endogenous nitric oxide synthase (eNOS) inhibitor. Its importance is becoming more recognised and further studies are required to determine its use in clinical diagnosis. Available evidence indicates that oxidative stress leads to changes in the activity of enzymes involved in the production and degradation of ADMA.[4,5] High levels of ADMA and low levels of nitric oxide (NO) in the coronary arteries of patients with vasospastic angina have been reported.[6]

In the cardiovascular system, NADPH oxidase accounts for the production of reactive oxygen species (ROS), which is produced not only during I/R injury but also under physiological conditions.[7] The pro-oxidative NADPH oxidase is present in the plasma membranes of neutrophils, which are an important source of free radical formation and I/R injury.[8] Additionally, the rhokinase pathway, which has an important role in regulation of vascular smooth muscle tone, has been shown to be involved in I/R injury, thus making its inhibition a potential target for limiting I/R injury.[9]

It has been reported that inflammatory NFkB expression increased in the I/R-related infarct area; inflammation was suppressed when NFkB expression was inhibited, and cardiac preservation was provided.[10] In this context, caveolin-1 was shown to regulate eNOS activation consistently with other signalling molecules such as hsp 90.[11] Interaction of hsp 90 with eNOS increases eNOS activity, and consequently, NO production increases.[12,13] Myocardial caveolin-1 content is reported to decrease following ischaemia–reperfusion.[14] Caveolin-1 deficiency was noted to aggravate cardiac dysfunction and reduce the survival rate in mice that had experienced myocardial infarction (MI).[15]

Rosuvastatin is a synthetic hydrophilic statin widely used in the treatment of dyslipidaemia, as it increases levels of high-density lipoprotein (HDL) cholesterol, and reduces low-density lipoprotein (LDL) cholesterol and triglyceride levels. Statins have been reported to have anti-inflammatory, antiproliferative, antithrombotic, anti-atherogenic and antihypertensive effects in addition to their cholesterol-lowering effects.[8,16-18] Recent studies indicate that rosuvastatin decreases levels of ADMA in hypercholesterolaemia,[19] levels of caveolin,[20] and also NFkB levels[21] in subaracnoid bleeding.

To our knowledge, the effects of rosuvastatin on ADMA, rhokinase, caveolin-1, hsp 90 and NFkB levels are not known in cardiac I/R injury. In this study, we aimed to investigate the influence of rosuvastatin on oxidative stress-related rhokinase, NADPH oxidase, ADMA, caveolin-1 and hsp 90 levels in a rat model of I/R injury.

Methods

Male Sprague Dawley rats weighing 250–300 g were kept in a quiet, temperature- (21 ± 2°C) and humidity- (60 ± 5%) controlled room in which a 12-hour light–dark cycle was maintained. All experiments were performed between 9:00 and 17:00.

The rats were divided into three groups: control (sham), I/R + vehicle (physiological saline) and I/R + rosuvastatin. Vehicle or rosuvastatin (10 mg/kg) were administered in the afternoon (17:00) by intraperitoneal injection for 15 days before ischaemia. I/R protocols were performed in the morning (08:00–12:00).

Measurement of myocardial tissue rhokinase, NADPH oxidase, caveolin-1, hsp 90, NFkB and ADMA levels were performed in seven animals in each group. Rosuvastatin (Abdi Ibrahim Pharmaceutical Co, Istanbul, Turkey) was dissolved in physiological saline.

All experiments in this study were performed in accordance with the guidelines for animal research from the National Institutes of Health and were approved by the local committee on animal research (FUHADYEK -13.06.2012-76).

Ischaemia–reperfusion procedure

Rats were anesthetised with urethane (1.2–1.4 g/kg) administered intraperitoneally. The jugular vein and trachea were cannulated for drug administration and artificial respiration, respectively. Systemic blood pressure (BP) was monitored via the carotid artery with a Harvard model 50-8952 transducer (Harvard Apparatus Inc, Massachusetts, USA) and displayed on a Harvard Universal pen recorder (Harvard Apparatus, Inc, Massachusetts, USA) together with a standard 12-lead ECG.

The chest was opened via a left thoracotomy, followed by sectioning the fourth and fifth ribs, about 2 mm to the left of the sternum. Positive-pressure artificial respiration was started immediately with room air, using a volume of 1.5 ml/100 g body weight at a rate 60 beats/min to maintain normal pCO_2, pO_2 and pH parameters.

After the pericardium was incised, the heart was exteriorised by gentle pressure on the outside of the rib cage. A 6/0 silk suture attached to a 10-mm micropoint reverse-cutting needle was quickly placed under the left anterior descending coronary artery. The heart was then carefully replaced in the chest, and the animal was allowed to recover for 20 min. Any animal in which this procedure produced arrhythmias or a sustained decrease in mean arterial BP to less than 70 mmHg was discarded.

A small plastic snare was threaded through the ligature and placed in contact with the heart. The artery could then be occluded by applying tension to the ligature, and reperfusion was achieved by releasing the tension. At the end of the experimental period, left ventricle myocardial samples, distal to the left main coronary artery occlusion, were collected for analysis and analysed within one month.

Quantitative real-time polymerase chain reaction analysis (qRT-PCR)

Tissue samples were immersed in RNAlater. After overnight saturation with RNAlater, the tissues were stored at –80°C. All protocols were performed according to the manufacturer's instructions. Total RNA was extracted from rat heart tissues using TRizol reagent (Invitrogen, Carlsbad, USA).

To carry out the PCR assay, total RNA from the heart samples in each experimental group was pooled (3 µg total). cDNA from the pooled samples was synthesised using a high-capacity RNA-to-cDNA kit (Invitrogen, Carlsbad, USA). Relative expression levels of mRNA were determined using a 7500 fast real-time PCR (PE Biosystems, Foster City, CA, USA) with Taq Man master mix and rat-specific assays for NFkB, caveolin-1, hsp 90 and GAPDH genes. The relative abundance of mRNA was calculated after normalisation to GAPDH.

Triplicate assays were performed. PCR reactions were performed after heating to 50°C for 2 min followed by 40 cycles of denaturation at 95°C for 10 min, 95°C for 15 sec and 60°C for 1 min. ADMA, rhokinase and NADPH oxidase levels were evaluated with ELISA.

Statistical analysis

Data are expressed as arithmetic means ± SEM. When $p < 0.05$, the difference was considered to be statistically significant. Normality of the distribution within the groups was evaluated with the Shapiro–Wilk test. Multiple comparisons between the experimental groups were performed by one-way analysis of variance with the Tukey *post hoc* test.

Results

I/R caused a significant increase in ADMA levels. This increase was limited although not statistically significantly attenuated in the rosuvastatin group (Fig. 1).

While NFkB levels increased 2.2-fold with I/R, they significantly decreased in the rosuvastatin-treated group (Fig.

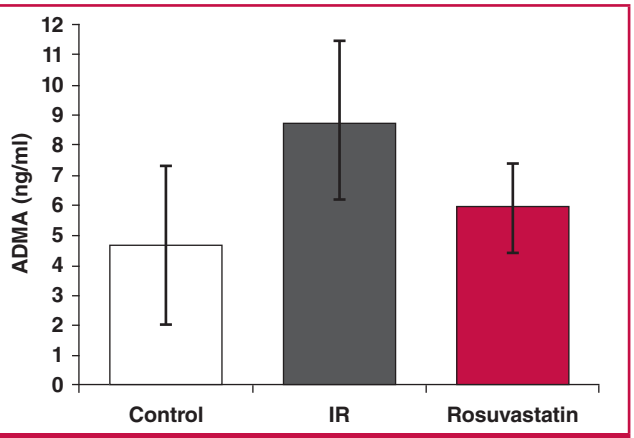

Fig. 1. Effect of rosuvastatin on ADMA levels in myocardial I/R. Vehicle or rosuvastatin (10 mg/kg) were administered by intraperitoneal injection for 15 days before ischaemia ($n = 7$ in each group). *$p < 0.05$ significantly different from control group (one-way analysis of variance followed by a *post hoc* Tukey HSD test).

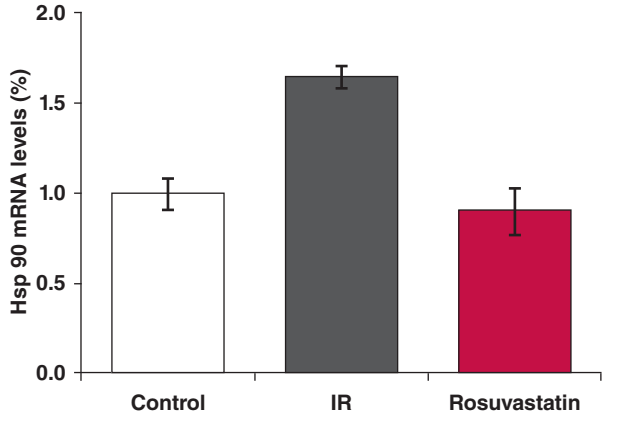

Fig. 3. Effect of rosuvastatin on hsp 90 mRNA levels in myocardial I/R. Vehicle or rosuvastatin (10 mg/kg) were administered by intraperitoneal injection for 15 days before ischaemia ($n = 7$ in each group). *$p < 0.05$ significantly different from control group and a; $p < 0.05$ significantly different from IR group (one-way analysis of variance followed by a *post hoc* Tukey HSD test).

2). While hsp 90 levels increased 1.6-fold in the I/R group, they decreased significantly in the rosuvastatin group and returned to control values (Fig. 3). There was no significant difference between groups in terms of caveolin-1 levels (Fig. 4).

NADPH oxidase levels significantly increased with I/R, and a limited but statistically significant attenuation was observed in only the rosuvastatin group (Fig. 5). Similarly, rosuvastatin treatment was able to significantly attenuate the increase in rhokinase levels (Fig. 6).

Discussion

Results from this study show that 15-day intraperitoneally injected rosuvastatin was able to decrease the myocardial injury caused by I/R. Ischaemia–reperfusion itself increased tissue NFkB, hsp 90, ADMA, and NADPH levels without significantly changing caveolin-1 levels. According to our results, rosuvastatin inhibited changes in levels of NFkB, hsp 90, rhokinase, ADMA and NADPH oxidase but not caveolin-1 levels in rat cardiac tissue with induced myocardial I/R.

The beneficial effects of statins have been shown in cardiovascular diseases, including acute coronary syndromes.[8,18,22] It was reported that rosuvastatin may have protective effects in I/R injury and these effects could have been mediated by immunomodulatory and anti-inflammatory effects.[7,17,23] Kuhn *et al.*[24] showed that myocardial function improved with rosuvastatin administration for seven days prior to cardiopulmonary bypass surgery. The protective effects of rosuvastatin regarding antioxidant and anti-inflammatory properties have also been reported in brain I/R models.[25]

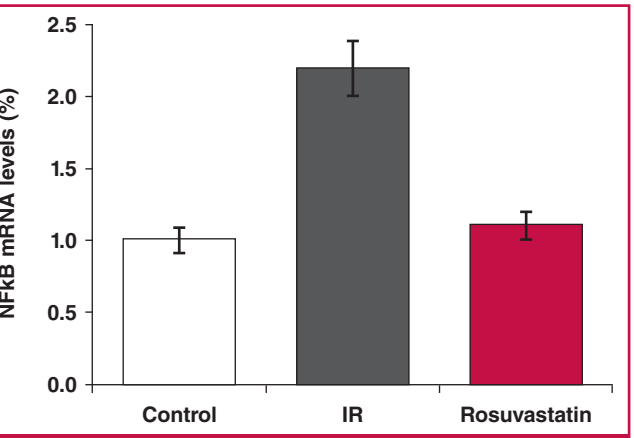

Fig. 2. Effect of rosuvastatin on NFkB mRNA levels in myocardial I/R. Vehicle or rosuvastatin (10 mg/kg) were administered by intraperitoneal injection for 15 days before ischaemia ($n = 7$ in each group). *$p < 0.05$ significantly different from control group and a; $p < 0.05$ significantly different from IR group (one-way analysis of variance followed by a *post hoc* Tukey HSD test).

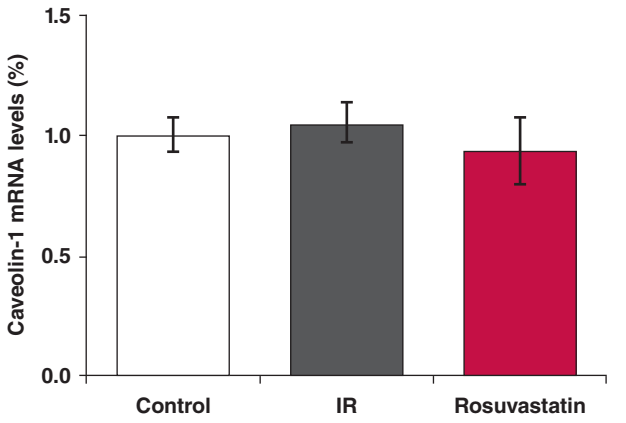

Fig. 4. Effect of rosuvastatin on caveolin-1 mRNA levels in myocardial I/R. Vehicle or rosuvastatin (10 mg/kg) were administered by intraperitoneal injection for 15 days before ischaemia (n = in 7 each group, one-way analysis of variance followed by a *post hoc* Tukey HSD test).

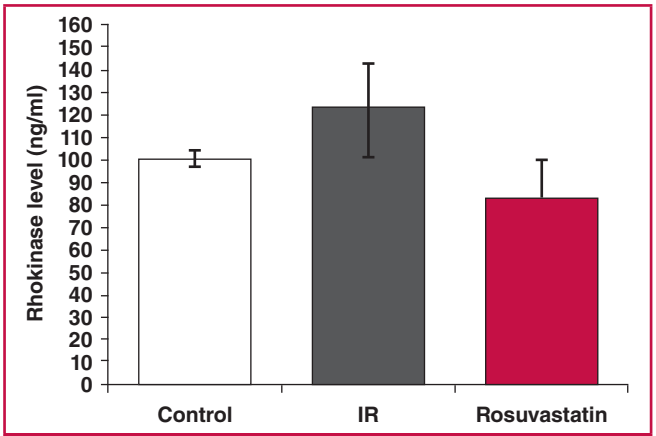

Fig. 5. Effect of rosuvastatin on rhokinase levels in myocardial I/R. Vehicle or rosuvastatin (10 mg/kg) were administered by intraperitoneal injection for 15 days before ischaemia (n = 7 in each group). a; $p < 0.05$ significantly different from IR group (one-way analysis of variance followed by a *post hoc* Tukey HSD test).

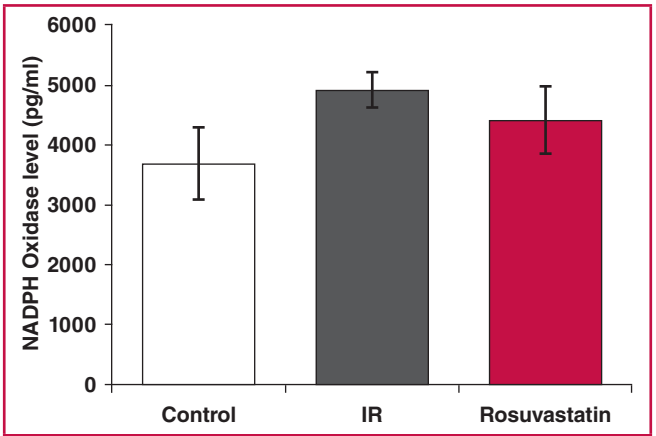

Fig. 6. Effect of rosuvastatin on NADPH oxidase levels in myocardial I/R. Vehicle or rosuvastatin (10 mg/kg) were administered by intraperitoneal injection for 15 days before ischaemia (n = 7 in each group). *$p < 0.05$ significantly different from control group (one-way analysis of variance followed by a *post hoc* Tukey HSD test).

ADMA is an endogenous NOS inhibitor competing with L-arginin to bind to NO. The plasma ADMA level was reported to be elevated in coronary artery disease and it is seen to be a risk factor with a worse clinical outcome for percutaneous coronary interventions.[26-28] Studies have consistently indicated that cardiac I/R caused elevation in levels of serum ADMA[29] and myocardial tissue ADMA.[30] In our study, tissue ADMA levels were elevated with I/R, which was reduced in the rosuvastatin group.

Elevated NADPH levels lead to elevation in ROS levels and decreased bioavailability.[7] NADPH oxidase activity was reported to increase in the heart with I/R. NADPH oxidase was shown to be related to platelet activation and thrombus formation in I/R.[8] In our study, the NADPH oxidase level increased with I/R and this elevation decreased with rosuvastatin administration.

Pignatelli *et al.*[8] demonstrated that rosuvastatin caused antiplatelet activity independent of its lipid-lowering effect and this was related to its effect of reducing NADPH oxidase levels. In the same study, rosuvastatin was shown to reduce oxidative stress by reducing NADPH oxidase levels, upregulating antioxidant enzymatic defence mechanisms and inhibiting hydrogen peroxide-mediated DNA damage.

Hsp 90 is a cytoprotective protein chaperone that participates in mitochondrial import of a number of proteins. It was shown to increase I/R-related necrotic cell death when blocked pharmacologically.[31] Hsps are reported to be protective by being upregulated in the case of increased oxidative stress.[32] Under our experimental conditions, the hsp 90 level was seen to increase as a protective mechanism during I/R. We believe that the expected increase in hsp 90 levels would not have been seen together with the decrease in injury due to the positive effects of rosuvastatin on the other parameters.

Caveolin-1 elevation has been shown to contribute to the pathology of cardiovascular diseases, and caveolin-1 peptide was reported to be protective for the heart in myocardial I/R. This effect involved a NO-mediated mechanism.[14] Caveolin-1 deficiency was shown to aggravate cardiac dysfunction and reduced survival rate in rats that experienced MI.[15] Although a significant change was not detected in caveolin-levels in our study, other studies are available indicating that myocardial caveolin-1 content decreased following I/R.[14]

In this experimental study, rhokinase levels were detected to increase following I/R. Rhokinase activity has been shown to increase during reperfusion and played an important role in I/R-related myocardial injury.[33] Animal studies have suggested that rhokinase inhibition protects the heart against I/R injury. Administration of the rhokinase inhibitor, Y-27632, significantly inhibited rhokinase activation in I/R and reduced the infarct area.[33] In the present study, rhokinase activity was observed to decrease when rosuvastatin was administered. Similarly, rhokinase activity could be inhibited in long-term administration of rosuvastatin and in cell cultures.[34-36]

NFkB is a redox-sensitive transcription factor that is activated in response to oxidative stress and is responsible for the production of inflammatory genes. Reduction in sensitivity to I/R injury in NFkB knock-out mice suggested that NFkB-mediated inflammatory responses play an important role in injury.[37] The area of the myocardial infarct induced by reperfusion decreased significantly when NFkB activation was blocked through PS-519.[38] Results of the study showed that reperfusion injury may be inhibited when NFkB activation is suppressed. In the present study, NFkB levels significantly increased with I/R. This increase was significantly reduced when rosuvastatin was administered, and the levels returned to control values.

Conclusion

The effect of chronic administration of rosuvastatin on oxidative stress, inflammation and endogenous NO generation in I/R injury has been reported for the first time in our study. Rosuvastatin caused inhibition of I/R-mediated increases in related mediators, although not significantly for ADMA and NADPH oxidase levels. We believe that rosuvastatin may be important in treatment protocols of myocardial I/R due to its positive effects on rhokinase, NADPH oxidase, ADMA, hsp 90 and NFkB levels, although further studies are necessary.

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Short-term outcomes after hospital discharge in patients admitted with heart failure in Abeokuta, Nigeria: Data from the Abeokuta Heart Failure Registry

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Abstract

Background: Compared to other regions of the world, there is a paucity of data on the short-term outcome of acute heart failure (AHF) in Africa's most populous country, Nigeria. We examined the six-month outcomes (including case fatalities) in 285 of 309 AHF subjects admitted with HF to a tertiary hospital in Abeokuta, Nigeria.

Methods: The study cohort of 285 subjects comprised 150 men (52.6%) and 135 women (47.4%) with a mean age of 56.3 ± 15.6 years and the majority in NYHA class III (75%).

Results: There were a number of differences according to the subject's gender; men being older and more likely to present with hypertensive heart disease (with greater left ventricular mass) while also having greater systolic dysfunction. Mean length of stay was 10.5 ± 5.9 days. Mean follow up was 205 days, with 23 deaths and 20 lost to follow up. At 30 days, 4.2% (95% CI: 2.4–7.3%) had died and by 180 days this had increased to 7.5% (95% CI: 4.7–11.2%); with those subjects with pericardial disease demonstrating the highest initial mortality rate. Over the same period, 13.9% of the cohort was re-admitted at least once.

Conclusions: The characteristics of this AHF cohort in Nigeria were different from those reported in high-income countries. Cases were relatively younger and presented with non-ischaemic aetiological risk factors for HF, especially hypertensive heart disease. Moreover, mortality and re-admission rates were relatively lower, suggesting region-specific strategies are required to improve health outcomes.

Keywords: heart failure, mortality, outcome, Abeokuta, Nigeria

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Heart failure (HF) has emerged as a global epidemic in at-risk populations, including those living in high-income countries and, as recently described, in low- to middle-income regions of the world, such as sub-Saharan Africa.[1-4] While there are well-established HF registries to capture both the characteristics and health outcomes among those hospitalised with AHF in Europe,[5,6] North America,[7,8] and the Asia–Pacific region,[3,9,10] there are few reports from sub-Saharan Africa.[11] This includes Nigeria (the most populous country in the region), where HF has emerged as a potentially large public health problem.[1]

Although there have been many therapeutic gains in the management of chronic HF,[12] leading to improved overall survival rates,[13] there has been very little parallel success (pending further evaluation of the recently reported RELAX trial[14] with regard to AHF). This is particularly important when one considers the high proportion of patients who still require hospitalisation for acute HF, and associated high levels of in-patient case fatality and poor short- to medium-term health outcomes.

Given the paucity of data describing health outcomes in unselected patients hospitalised with AHF in Nigeria (and indeed the wider sub-Saharan Africa), we examined short- (30 days) to medium-term outcomes (180 days) in consecutive subjects with AHF recruited into the Abeokuta HF registry over a period of six months. Standardised data collected via the registry were used to both describe the baseline characteristics of the cohort and identify correlates of mortality during the six-month follow up.

Methods

The Abeokuta HF registry was a hospital-based, single-centre, prospective, observational study that consecutively recruited 285 subjects with *de novo* AHF and 24 cases of decompensated HF (acute-on-chronic HF), all admitted during the period 1 January 2009 to 31 December 2010. The 24 cases of decompensated HF were excluded from the final analysis.

The main objective of the registry was to characterise the current profile of HF in the community. It was also aimed at determining the mode of care as well as intra-hospital and six-month outcomes.

Clinical information relating to the socio-demography, medical history, signs and symptoms, medications, results of laboratory investigations, including 12-lead ECG and echocardiography, were collected. A standardised case report form was used for data collection. Home addresses and telephone contacts of the subjects as well as their next of kin were also recorded.

Subjects were weighed without shoes and in light clothing using a standard beam balance. An anthropometric plane was used for height measurement to the nearest centimetre. Body mass index (BMI) was calculated using the standard formula. Blood pressure measurements were done according to international guidelines,[15] with the use of a mercury sphygmomanometer (Accousson, London).

We defined anaemia as haematocrit of less than 10 g/dl. The modification of diet in renal disease (MDRD) formula was used for the estimation of glomerular filtration rate (GFR).[16] An estimated GFR (eGFR) of less than 60 ml/min/1.73 m^2 was the criterion used for defining renal dysfunction.[4]

A clinical diagnosis of HF was based on the Framingham criteria.[17] Using the recent guidelines of the European Society of Cardiology,[18] subjects were categorised into *de novo* presentation, as well as recurrent presentation of typically decompensated HF (i.e. acute-on-chronic HF).

Standard 12-lead resting ECGs were recorded for each patient using a Schiller ECG machine (Schiller AG, Switzerland). All the 12-lead resting ECGs were performed by trained nurses/technicians and analysed by a reviewer who was blinded to the clinical data of the patients.

Echocardiography was performed on the subjects with the use of an Aloka SSD – 4000 echocardiography (Aloka Co Ltd, Tokyo, Japan). Standard views and two-dimensional guided M-mode measurements were obtained according to international guidelines. Aortic root and left atrial diameter, left ventricular (LV) internal dimensions and wall thicknesses were obtained according to the American Society of Echocardiography (ASE) criteria. Measurements were obtained in up to three cycles and averaged. One experienced cardiologist (OSO) performed all the procedures.

In our laboratory, the intra-observer concordance correlation coefficient and measurement errors have been reported.[19] The Devereux and Recheck formula was used for LV mass calculation.[20] Increased relative wall thickness (RWT) was defined as RWT > 0.43.[21]

Impaired LV systolic function was defined as LV ejection fraction of < 50%. Transmitral flow velocities, deceleration time and isovolumic relation time were obtained using standard methods.[22] Tissue Doppler imaging (TDI) was applied only to identify true pseudo-normalised filling pattern.

The cohort was prospectively followed up for six months. The mean follow-up period was 205 days. Subjects were contacted via clinic visits or telephone calls at one, three and six months. Follow-up data included their wellbeing, medications, history of rehospitalisation and deaths (from next of kin). In addition to patient or relative telephone interviews, where necessary, referring physicians were contacted for additional information. Fig. 1 is a flow chart showing the recruitment and follow up of the study cohort.

We examined (1) length of hospital stay (LoS), (2) Survival status on discharge (dead or alive), (3) short-term case fatality/re-admission (30 days), (4) medium-term case fatality (within 180 days), (5) rehospitalisation status (within 180 days), and (6) event-free survival from re-admission or death.

The study was reviewed and approved by the institution's ethics review board. All the subjects gave informed consent and the study was carried out in accordance with the Declaration of Helsinki.[23]

Statistical analysis

Data were entered into EpiData software. The EpiData association (att. Jens Lauritsen, Enghavevej 34, DK5230 Odense M, Denmark) was used for data entry, while SPSS version 15 and Stata version 11.1 were used for data cleaning and analysis. Continuous variables are presented as means and standard deviations (SDs), or medians with their 25th and 75th percentiles when the distribution of the data did not follow Gaussian distribution.

Categorical variables are displayed as frequencies and proportions. Group comparison was done with the Student's *t*-test, and chi-square statistics were used for comparison of categorical variables. Survival function estimates were performed using the Kaplan–Meier method and the difference was tested using the log-rank test. The follow up was censored at six months post admission.

Predictors of survival were determined using univariate regression analyses. Thereafter multiple logistic regression analysis was performed to identify independent predictors of survivals ($p < 0.1$ used for selection of variables).

Results are expressed as odds ratio (OR) with their 95% confidence intervals (95% CI). Odds ratios that were significantly greater than 1.00 implied that subjects with that attribute had higher risks of death compared to subjects who did not. A *p*-value of < 0.05 was taken as significant.

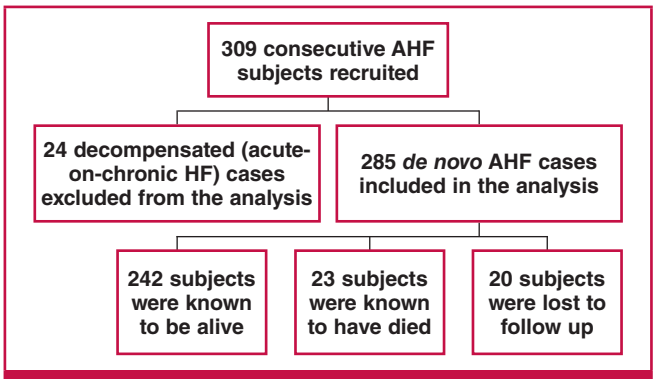

Fig. 1. Flow chart showing the recruitment of the subjects.

Results

Overall, there were 150 men (52.6%) and 135 (47.4%) women (Table 1). The mean age was 56.3 ± 15.6 years (57.0 ± 13.6 and 55.4 ± 17.6 years for men and women, respectively) with 46% aged ≥ 60 years. Around one-third had no formal education, two-thirds were married and most (75.8%) were urban residents. The majority of the subjects were in NHYA class III (75.4%).

The women were more likely not to have had formal education (43.7 vs 26.0%, $p = 0.029$), more likely not to be a smoker (96.3 vs 68.7%, $p < 0.001$), and less likely to be a current alcohol user (2.2 vs 9.3%, $p < 0.001$). Alternatively, men had higher rates of hypertension (85.3 vs 77.0%) and chronic obstructive pulmonary disease (COPD) (7.3 vs 6.7%).

Table 2 shows the laboratory profile, aetiological risk factors and discharge medications. Serum urea and creatinine concentrations were significantly higher in men than women.

Except for peripartum cardiomyopathy (PPCM), the aetiological risk factors were similar in men and women. Hypertensive heart disease was found in 75.8% of patients, dilated cardiomyopathy in 8.4%, cor pulmonale in 5.6%, pericardial diseases in 3.2% and rheumatic heart disease in 2.5%. PPCM, thyroid heart disease, coronary artery disease and endomyocardial fibrosis were found in 2.1, 1.1, 0.4, 0.4 and 0.7% of patients, respectively.

The discharge medications were similar in men and women except for beta-blockers, which were prescribed more in men.

Table 3 depicts the 12-lead ECG and echocardiographic parameters according to gender. Men had significantly higher mean absolute QT intervals (374 ± 35.0 vs 348 ± 45.5 ms, $p = 0.006$), left atrial area (28.8 ± 8.8 vs 25.0 ± 6.4 cm^2, $p = 0.010$), LV internal dimension in systole, as well as absolute and indexed LV mass ($p = 0.001$, 0.026 and 0.016, respectively). On the other, hand women had significantly higher ejection fractions (45.1 ± 20.1 vs 40.6 ± 23.6, $p = 0.007$).

The mean length of hospital stay was 10.5 ± 5.9 days, (11.0 ± 5.4 and 10.0 ± 6.3 days for women and men, respectively). Mortality rate at 30 days was 4.2% (95% CI: 2.4–7.3) for the whole cohort. It was 3.9% (95% CI: 1.7–8.5%) and 4.5% (95% CI: 2.1–9.3%) for men and women, respectively. At 180 days, the mortality rate was 7.3% (95% CI: 4.7–11.2%). This was 7.1% (95% CI: 3.8–12.7%) and 7.5% (95% CI: 3.9–14.0%) for men and women respectively.

Patients with pericardial diseases had the highest early mortality rate. Hypertensive HF subjects had the best survival rates (Figs 1–3). At 180 days, 13.9% of the subjects were rehospitalised at least once (14.6% for women and 13.3% for men).

Table 4 shows the univariate correlates of survival in the cohort. Mortality was associated with female gender, being single, HF with normal ejection fraction, lower blood pressure, higher heart and respiratory rates, higher body temperature, anaemia, high creatinine levels and higher total white blood cell counts. Other factors included higher QRS duration and corrected QT interval, larger left atrial diameter and area, higher

Table 1. Demographic and clinical profile characteristics of the cohort.

Variable	*All* (n = *285*)	*Men* (n = *150*)	*Women* (n = *135*)	p-*value*
Socio-demographic variables				
Age (years)	60.0 ± 13.2	57.0 (13.6)	55.6 (17.3)	0.382
Age > 60 years (%)	46.3	48.7	43.7	0.425
No education	98 (34.4)	39 (26.0)	59 (43.7)	0.028
Married (%)	156 (67.8)	92 (73.0)	64 (61.0)	0.014
Unemployed	7 (2.3)	1 (0.6)	6 (4.2)	0.007
Urban residence	216 (75.8)	113 (75.3)	103 (76.5)	0.389
Risk factors and co-morbidities				
Never smoked cigarettes	233 (81.8)	103 (68.7)	103 (96.3)	< 0.001
Current alcohol use	17 (6.0)	14 (9.3)	3 (2.2)	< 0.001
Diabetes mellitus	37 (13.0)	19 (12.7)	18 (13.3)	0.735
Hypertension	232 (81.4)	128 (85.3)	134 (77)	0.103
COPD	20 (7.0)	11 (7.3)	9 (6.7)	0.923
Family history of heart disease	25 (8.8)	9 (6.0)	16 (11.9)	0.240
Clinical/laboratory parameters				
NYHA class				
Class II	24 (8.4)	16 (10.7)	8 (5.9)	0.212
Class III	215 (75.4)	107 (71.3)	108 (80.0)	
Class IV	46 (16.1)	27 (18.0)	19 (14.1)	
BMI (kg/m^2)	25.2 ± 5.7	24.1 (5.0)	23.7 (5.5)	0.527
Systolic BP (mmHg)	131.9 ± 25.1	137.9 (30.0)	133.3 (27.9)	0.253
Diastolic BP (mmHg)	85.4 ± 15.9	89.0 (19.6)	85.3 (17.1)	0.156
Pulse pressure (mmHg)	46.5 ± 15.7	49.0 (19.0)	47.7 (16.6)	0.527
Respiratory rate (cycles/min)	30.2 ± 6.5	28.5 ± 6.4	27.9 ± 6.7	0.541
Pulse rate (bpm)	95.9 ± 16.7	96.2 ± 18.2	96.3 ± 17.8	0.527
Packed cell volume (%)	35.9 ± 7.8	37.5 ± 7.2	36.8 ± 7.7	0.541
Total white blood cell count (× 10^9 cells/l)	6.4 ± 2.9	7.3 ± 3.7	7.4 ± 3.8	0.933
Serum sodium (mmol/l)	136.5 ± 6.4	135.9 ± 6.7	136.3 ± 6.1	0.134
Serum potassium (mmol/l)	3.7 ± 0.8	3.7 ± 0.8	3.6 ± 0.8	0.461
Total cholesterol (mg/dl)	162.5 ± 53.3	157.7 ± 84.0	181.2 ± 64.6	0.213
Serum glucose (mg/dl)	111.7 ± 53.2	115.6 ± 50.6	114.0 ± 58.5	0.845
Serum urea (mg/dl)*	38.5 ± 30.0	50.5 ± 51.4	36.1 ± 29.7	0.020
Serum creatinine (mg/dl)*	1.8 ± 0.4	1.7 ± 2.5	1.2 ± 1.4	0.093

COPD = chronic obstructive pulmonary disease.

Table 2. Aetiology of HF and discharge medications in the 285 subjects.

Variable	*All* (n = *285*)	*Men* (n = *150*)	*Women* (n = *135*
Aetiology of HF, *n* (%)			
Hypertension	216 (75.8)	119 (79.3)	97 (71.9)
Dilated cardiomyopathy	24 (8.4)	16 (10.7)	8 (5.9)
Cor pulmonale	16 (5.6)	9 (6.0)	7 (5.2)
Pericardial diseases	9 (3.2)	1 (0.7)	8 (5.9)
Rheumatic heart disease	7 (2.5)	4 (2.7)	3 (2.2)
Peripartum cardiomyopathy	6 (2.1)	0 (0.0)	6 (4.4)
Thyroid heart disease	3 (1.1)	0 (0.6)	3 (2.2)
Ischaemic heart disease	1 (0.4)	1 (0.7)	0 (0.0)
Adult congenital heart disease	1 (0.4)	0 (0.0)	1 (0.7)
Endomyocardial fibrosis	2 (6.7)	0 (0.0)	2 (0.7)
Type of heart failure			
Systolic heart failure (%)	66.4	71.4	60.9
Heart failure with normal EF (%)	33.6	28.6	39.1
Medications, *n* (%)			
Loop diuretics	249 (87.4)	132 (88.0)	117 (86.7)
Digoxin	219 (76.8)	114 (76.0)	105 (77.8)
ACE inhibitors/ARBs	281 (98.6)	148 (98.7)	133 (98.5)
Beta-blockers	56 (19.6)	35 (23.3)	21 (15.6)
Spironolactone	247 (86.7)	133 (87.3)	116 (85.9)
Hydrallazine–isosorbide	33 (11.7)	19 (12.9)	14 (10.4)
Amiodarone	5 (1.8)	4 (2.7)	1 (0.7)

Table 3. Twelve-lead ECG and echocardiographic profile according to gender.

Variable	*All (n = 285)*	*Men (n = 150)*	*Women (n = 135)*	*p-value*
Ventricular rate (bpm)	96.3 ± 22.5	94.3 ± 17.3	101.3 ± 21.8	0.110
QRS duration (ms)	116.0 ± 26.2	117.1 ± 24.5	107.8 ± 41.1	0.213
QT interval (ms)	350.7 ± 30.6	374.3 ± 35.0	348.8 ± 45.5	0.006
Corrected QT (ms)	442.0 ± 20.9	462.2 ± 38.2	447.6 ± 36.2	0.085
Atrial fibrillation (%)	13.3	16.7	9.6	0.337
Aortic root diameter (cm)	3.2 ± 0.6	3.26 ± 0.58	2.84 ± 0.38	< 0.001
Left atrial diameter (cm)	5.9 ± 0.8	4.75 ± 0.89	4.50 ± 0.85	0.176
Left atrial area (cm^2)	30.15 ± 9.91	28.8 ± 9.0	24.7 ± 6.3	0.010
IVSD (cm)	1.18 ± 0.28	1.33 ± 0.39	1.23 ± 0.32	0.393
LVPWd (cm)	1.38 ± 0.35	1.19 ± 0.39	1.10 ± 0.35	0.116
LVIDd (cm)	5.52 ± 0.97	5.81 ± 1.61	5.16 ± 1.45	0.353
LVIDs (cm)	4.51 ± 1.57	4.80 ± 1.63	4.16 ± 1.43	0.001
Fractional shortening (%)	14.5 ± 2.97	17.77 ± 13.10	19.80 ± 12.21	0.060
Ejection fraction (%)	36.8 ± 6.53	40.57 ± 23.61	45.12 ± 20.11	0.007
E/A ratio	2.11 ± 1.55	2.14 ± 1.47	1.90 ± 1.25	0.199
DT (ms)	145.8 ± 59.2	144.2 ± 58.3	147.9 ± 60.5	0.480
IVRT (ms)	111.0 ± 34.3	114.9 ± 35.8	106.1 ± 32.1	0.127
LV mass (absolute)	449.0 ± 217.5	561.7 ± 106.6	233.0 ± 54.24	0.026
LV mass (indexed)	274.1 ± 117.5	336.4 ± 46.6	160.9 ± 16.1	0.016
Mitral regurgitation (%)	19.6	18.7	20.7	0.894
Tricuspid regurgitation (%)	15.1	12.7	17.8	0.459

IVSD = interventricular septal wall thickness in diastole, LVPWd = left ventricular posterior wall thickness in diastole, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, DT = deceleration time, IVRT = isovolumic relaxation time.

NYHA class and presence of tricuspid and mitral regurgitation. In a multiple regression analysis for predictors of mortality at 180 days, none of these variables reached statistical significance.

Discussion

This is the first detailed study of the clinical profile and short- or medium-term outcome of AHF cases in southern Nigeria.

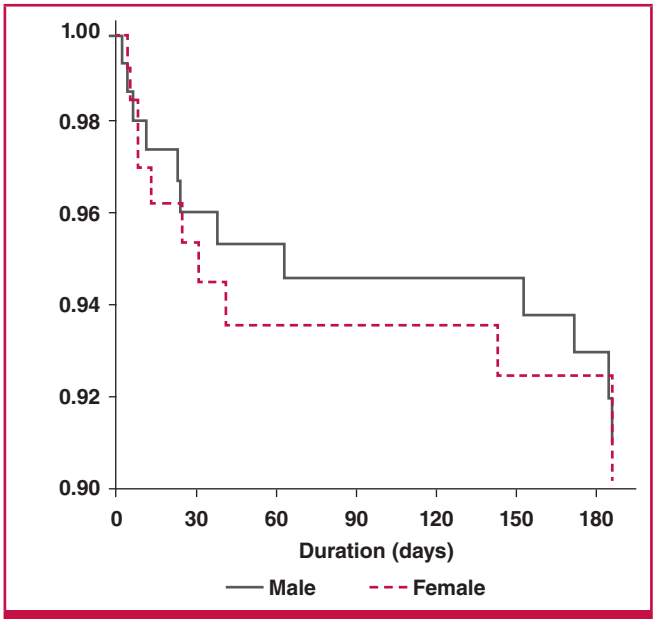

Fig. 2. Kaplan–Meier survival curve for males and females.

Similar to our earlier observation,[24] AHF in our community predominantly affects younger and middle-aged individuals who are in the prime of their lives. Hypertensive heart disease and other non-ischaemic aetiology contribute to over 90% of the cases.

The majority of our subjects presented with *de novo* acute HF. Our findings with the use of some disease-modifying agents such as angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), aldosterone antagonists (except for beta-blockers and hydralazine–isosorbide combination) are remarkably similar to findings in many other parts of the world.[6,8] Mortality rates in the short and medium term are relatively low, and higher in women than men.

Our findings of relatively young age at presentation for AHF is similar to reports from many parts of Africa.[1,4,25] AHF patients on the continent are about 20 years younger than similar patients in high-income countries.[6-9] This implies that HF afflicts our population in their productive years, with attendant economic loss to the society and greater disability-adjusted life years.

The comparable or even lower short- or medium-term mortality rate of HF in our cohort compared to findings in high-income countries is an important observation from this study.[7,8] Mortality rates in our study were 4.2% (95% CI: 2.4–7.3%) and 7.3% (95% CI: 14.7–11.2%) at 30 days and 180 days, respectively.

Unlike findings in high-income countries,[26,27] we noted that age was not associated with poorer outcome in our cohorts. Our finding of a better prognosis in obese individuals is similar to that of other researchers.[27,28] In the Framingham study, high BMI was associated with a better prognosis (HR for mortality per one SD: 0.88, 95% CI: 0.75–1.04 for men, and 0.86, 95% CI: 0.72–1.03 for women). This may also be consistent with the 'obesity paradox' in HF.[29-31] Underweight in HF patients may be indicative of cardiac cachexia, and progression of HF and poor prognosis.

Lower blood pressure or pulse pressure was associated with a poorer outcome. This may reflect advanced HF and decreased stroke volume. This has been noted in previous studies.[26,32]

It is now well known that impaired renal function is an important predictor of all-cause mortality in HF.[33-35] This is similar

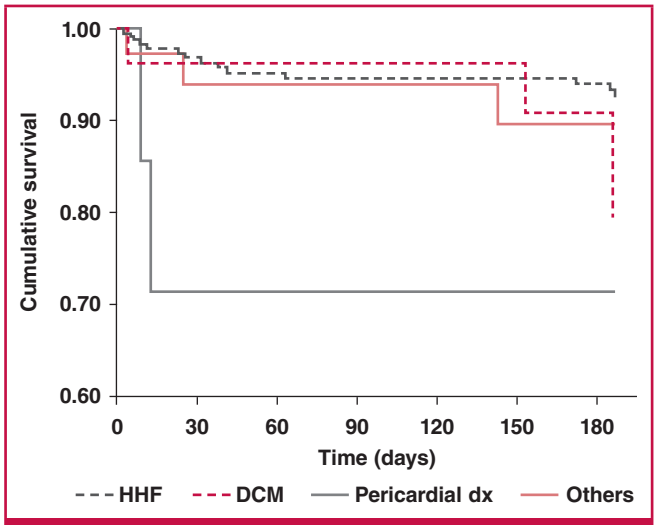

Fig. 3. Kaplan–Meier survival curve for the different aetiological risk factors.

Table 4. Clinical and demographic predictors of outcome on univariate analysis (six-month survival).

Variable	*All (n = 285)*	*Alive (258)*	*Dead (23)*	*OR*	*95% CI*	p-*value*
Age (years)	57.3 ± 15.4	57.4 ± 14.0	57.2 ± 19.1	0.99	0.96–1.01	0.324
Female gender (%)	52.6	54.5	50	1.14	0.48–2.70	0.764
No education (%)	33.3	32.8	30.0	0.77	0.26–2.28	0.635
Not married (single) (%)	67.8	69.6	52.9	1.51	0.56–4.07	0.417
Body mass index	24.0 ± 5.4	23.7 ± 4.9	23.4 ± 3.6	0.97	0.87–1.08	0.580
Non-smoker (%)	81.8	82.3	85.0	1.51	0.43–5.34	0.521
Alcohol use (%)	6.0	5.6	5.0	0.79	0.32–1.95	0.609
Presence of diabetes (%)	13.0	13.1	10.0	0.65	0.14–2.92	0.574
Respiratory rate (bpm)	28.3 ± 6.2	28.0 ± 6.6	29.2 ± 5.3	1.02	0.96–1.08	0.639
Heart rate (bpm)	95.5 ± 17.1	95.0 ± 17.4	100.5 ± 15.9	1.00	0.97–1.03	0.846
SBP (mmHg)	136.1 ± 29.4	137.3 ± 27.7	122.5 ± 20.0	0.98	0.96–6.99	0.017
DBP (mmHg)	87.1 ± 29.4	88.6 ± 18.7	80.0 ± 13.4	0.98	0.95–1.00	0.085
Pulse pressure > 30 mmHg (%)	3.3	2.1	5.0	0.42	0.16–1.10	0.078
NYHA (III, IV) (%)	91.5	90.4	95.0	4.03	1.53–10.65	0.005
Serum sodium (mmol/l)	136.9 ± 4.6	136.0 ± 6.4	137.2 ± 7.4	1.03	0.96–1.11	0.428
Serum potassium (mmol/l)	3.7 ± 0.5	3.6 ± 0.7	4.0 ± 1.0	1.64	0.72–3.75	0.243
Blood glucose (mg/dl)	112.3 ± 56.0	117.0 ± 58.5	111.8 ± 58.5	1.00	0.99–1.01	0.501
Packed cell volume (%)	41.0 ± 7.6	37.6 ± 7.0	32.2 ± 8.4	0.92	0.86–0.97	0.004
Total white blood cell count	6.8 ± 3.1	6.9 ± 3.4	9.2 ± 5.1	1.13	1.02–1.25	0.024
Serum creatinine (mg/dl)	0.8 ± 0.3	1.2 ± 1.0	2.1 ± 2.5	1.38	1.04–1.83	0.024
QRS duration (ms)	107.1 ± 9.4	110.3 ± 29.5	110.9 ± 32.2	1.01	0.99–1.03	0.171
Corrected QT (ms)	439.4 ± 40.9	449.3 ± 34.4	457.3 ± 34.6	1.01	0.99–1.04	0.173
Atrial fibrillation (%)	13.3	14.6	20.0	1.14	0.36–3.55	0.827
E/A ratio	2.2 ± 1.0	2.1 ± 1.3	2.7 ± 1.6	1.40	0.99–1.97	0.060
Left atrial area (cm^2)	26.2 ± 6.7	26.8 ± 7.5	34.2 ± 12.1	1.11	1.01–1.21	0.025
Left atrial diameter (cm)	4.8 ± 0.9	4.6 ± 0.9	5.0 ± 1.1	1.56	0.94–2.60	0.084
LVID (cm)	5.47 ± 1.55	5.6 ± 1.5	5.7 ± 1.2	1.11	0.74–1.67	0.614
HF with systolic dysfunction	66.4	67.5	70.6	0.66	0.27–1.59	0.356
MR (yes) (%)	19.6	20.2%	25.0	1.34	0.50–3.60	0.562
TR (yes) (%)	15.1	13.1%	35.0	2.64	1.00–6.95	0.050

SBP = systolic blood pressure, DBP = diastolic blood pressure, LVID = left ventricular internal diameter, MR = mitral regurgitation, TR = tricuspid regurgitation.

to the observation in our study. Patients with renal impairment often develop cardio-renal syndrome, which is caused by low cardiac output. These patients often develop multiple alterations at the vascular level, leading to endothelial dysfunction, coagulation abnormalities, insulin resistance, hyperhomocystinaemia and activation of the sympathetic nervous system, as well as the renin–angiotensin and aldosterone system. They are prone to unstable HF and susceptible to high catecholamine levels. Furthermore HF patients with renal dysfunction are also less likely to receive proven medications for HF.

Hyponatraemia and hypokalaemia were associated with a better prognosis in our study. This is contrary to most reports from the Western world, although in a Polish study, Biegus *et al.*[8] reported that hypokalaemia was associated with a better outcome. This may be related to better response to diuretics in the survivors, leading to the electrolyte derangement. It may also be speculated that sodium may play a lesser role in the pathophysiology of HF in our setting.

We also observed that left atrial size, left atrial area, left ventricular size, higher E/A ratio and presence of mitral and tricuspid regurgitation were associated with poorer outcomes. This has been well recognised by earlier studies.[7,9] Left atrial or ventricular size reflects left atrial or ventricular pressure and volume overload, and the severity and duration of increases in LV filling in response to cardiac functionl abnormality associated with HF.[36]

A plausible reason for the younger age at presentation for HF in our study and many parts of Africa may be related to the aetiology of the condition, which is conditions that present in young and middle age (for example rheumatic heart disease and cardiomyopathies). In addition, hypertension and related target-organ damage present at a younger age in Africans and people of African descent.

The dominance of *de novo* presentation of HF in our cohort may be related to poorer long-term outcome of HF in our setting, that is, few people are living with chronic HF. Another reason may be because of poor or inadequate health education. Most often patients do not keep to one health facility when they have chronic illnesses such as HF. They often move from one facility to another (including alternative healthcare facilities) seeking a cure.

The relatively low mortality rate in our cohort may be related to the fact that the study was conducted in a cardiology unit and may not reflect what happens in a general medical ward or in private practice in the country. The clinical characteristics of our patients may also be explanatory. Our subjects were younger compared to the typical patients with HF in the Western world, who are generally elderly.

The average length of hospital stay was longer in our setting (nine days) compared to 6.1 days in the USA[28] and nine days in Europe.[7] However it was shorter than the 21 days reported from Japan.[37] It is possible that longer stay in hospital affords patients the opportunity to recover well and get used to medications for HF. HF outcome is generally better in Japanese patients compared to other high-income countries.[7,8,10]

Furthermore it is also possible that the aetiology of HF in our cohort could have affected the outcome. Hypertension is predominantly the major risk factor for HF in our cohort. Ischaemic heart disease is relatively uncommon. It is well known that mortality rates from coronary artery disease (CAD) are generally worse than in those with non-ischaemic heart disease. Mitchell *et al.*[38] reported a total mortality rate of 30% at three years in the placebo group of ischaemic HF patients compared to a rate of 15% in the non-ischaemic HF group.

The poorer outcome of women in our study may be because the women were less educated and more likely to be unemployed and dependent than the men, and may not be able to pay for HF medications. Clinic follow up may also be poorer in the women.

The finding of low frequency of use of some disease-modifying drugs in our cohort is an opportunity for future

intervention in HF management in our environment. This is because studies have shown that ACE inhibitors,[39] ARBs,[40] and beta-blockers[12] can improve survival in patients with HF. Furthermore, the African-American Heart Failure trial has shown the efficacy of the hydrallazine–isosorbide combination in the treatment of HF in blacks.[13]

The main aetiological factors for HF in our cohort were non-ischaemic in origin, with hypertensive heart disease being responsible for over 75% of cases. It may be reasonable to suggest that applying guidelines derived from clinical trials in the Western world, where most HF is ischaemic in origin, may be inappropriate in our population.

Limitations

Our study was a single-centre, hospital-based study conducted in a cardiology unit and therefore may not have captured all the patients with heart failure in the city during the study period, although many referrals were received from surrounding hospitals and clinics during the period due to the awareness that was created of the study. The findings of the study may not be extrapolated to the general population or the situation in other Nigerian hospitals. A national HF registry is needed, as has been done in many other countries.

The use of the Framingham criteria as a screening tool may have missed some patients, especially the elderly with HF, as the criteria are not sensitive in this population.

Due to cost consideration, our subjects did not have NT-proBNP levels done as this has not become a routine practice in the country. NT-proBNP has been shown to be a strong predictor of prognosis in HF.[41] Other prognostic variables, such as exercise capacity (VO_2 and six-minute walk) were also not assessed in our patients.

Some of our patients were lost to follow up and this may have affected the survival information in this study. However the rate of attrition was similar to that in other follow-up studies.[8,11] This was complicated by the fact that there is no effective national death registry in the country. We also could not ascertain the exact cause of death for patients who died outside the hospital environment.

Conclusions

The characteristics of the HF population in Nigeria are different from similar populations in high-income countries. Our patients are about 20 years younger and have non-ischaemic aetiological risk factors for HF, especially hypertensive heart disease. Short- or medium-term outcome is relatively lower than (or comparable to) findings from high-income countries and have some similar prognostic factors, such as renal function, anaemia, body mass index, blood pressure parameters, as well as ECG and echocardiographic variables. There is a need for a national HF registry in the country to better understand the characteristics, management and outcome of HF in the different regions of the country.

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Thrombolysis risk prediction: applying the SITS-SICH and SEDAN scores in South African patients

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Abstract

At present, the only specific medical treatment for acute ischaemic stroke is intravenous administration of recombinant tissue plasminogen activator within 4.5 hours of stroke onset. In the last year, two scores for risk stratification of intracranial haemorrhage have been derived from multicentric European trial groups, the Safe Implementation of Treatment in Stroke – Symptomatic IntraCerebral Haemorrhage risk score (SITS-SICH) and the SEDAN score. The aim of this study was to pilot their use in a cohort of patients treated at a South African tertiary hospital.

Prospectively collected data were used from a cohort of 41 patients who underwent thrombolysis at Groote Schuur Hospital from 2000 to 2012. Computerised tomography brain imaging was available for review in 23 of these cases. The SITS-SICH and SEDAN scores were then applied and risk prediction was compared with outcomes.

Two patients suffered symptomatic intracranial haemorrhage (SICH), representing 4.9% (95% CI: 0–11.5%) of the cohort. This was comparable to the SICH rate in both the SITS-SICH (5.1%) and SEDAN (6.5%) cohorts. Patient scores in the Groote Schuur Hospital cohort appeared similar to those of the validation cohorts of both SITS-SICH and SEDAN.

With increasing use of thrombolysis in a resource-constrained setting, these scores represent a potentially useful tool in patient selection of those most likely to benefit from intravenous thrombolysis, reducing risk for SICH and with the added benefit of curtailing cost.

Keywords: stroke, acute ischaemic stroke, thrombolysis, intracranial haemorrhage, risk, SEDAN, SITS-MOST, rTPA, recombinant tissue plasminogen activator, Safe Implementation of Treatment in Stroke – Symptomatic IntraCerebral Haemorrhage risk score, South Africa, Groote Schuur Hospital

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Stroke is the most common cause of death in people over the age of 50 years in South Africa.[1] It is estimated that there were approximately 75 000 new cases of stroke in South Africa in 2008. Of these, approximately 25 000 were fatal within the first 28 days. In 2007, there were 350 000 people living with stroke in South Africa, of whom 35% had moderate to severe disability as a result of their stroke. [2]

Currently, intravenous (IV) administration of recombinant tissue plasminogen activator (tPA) within 4.5 hours of symptom onset is the only medical therapy shown to improve outcomes in acute ischaemic stroke.[3-5] It has become the standard of care in many international stroke centres.

However, it is still unclear which patients are most likely to benefit and in what treatment time frame. Initial evidence demonstrated the benefit of thrombolysis in selected patients presenting within three hours. It has subsequently been shown that the window of maximum beneficial effect extends to 4.5 hours.[6,7]

Careful selection of patients suitable for thrombolysis treatment is required to maximise the benefit obtained and offset the risk of clinical deterioration due to symptomatic intracranial haemorrhage. Observational data from SITS-MOST show thrombolysis to be as safe and effective in real clinical practice as in clinical trials; however, the rate of SICH remained between 1.7 and 4.6%.[8] It has been estimated that of 100 patients treated with tPA, one will have a severely disabling or fatal outcome due to tPA-related intracranial haemorrhage. [9]

In 2011, Wasserman and Bryer published data on a cohort of 42 patients treated with tPA at a tertiary hospital in Cape Town, which showed comparable safety and early outcomes to similar cohorts in both developed and developing countries.[10] Many clinicians however remain concerned about the use of this treatment modality and the risk of SICH.[11]

Two scoring systems that attempt to stratify patients by their risk of developing SICH following thrombolysis have recently been derived from multicentre cohorts of patients – the Safe Implementation of Treatment in Stroke – Symptomatic IntraCerebral Haemorrhage risk score (SITS-SICH)[12] and the SEDAN score.[13] The SITS-SICH score is derived from the SITS-MOST patient cohort and was internally validated on a random sample of more than 15 000 patients; it incorporates primarily clinical variables which best predict the SICH following thrombolysis with tPA. The SEDAN score is based on both clinical and radiological findings on computerised tomography (CT) of the brain, and was externally validated in a smaller cohort of 828 patients.

Both scores however have been validated in European populations in developed countries and their utility in a different setting is not known. Accurate assessment of risk is necessary for clinicians to select patients who will most benefit from thrombolytic therapy, at the lowest risk of bleeding complications such as SICH. In a resource-constrained setting in which the cost

of thrombolytic therapy is significant, the inclusion of a risk-prediction score to the protocol used for treatment may improve the cost–benefit ratio, and optimise the allocation of scarce resources.

The aim of this pilot study was to evaluate the performance of both the SITS-SICH and SEDAN scores in predicting the risk of SICH in a Groote Schuur thrombolysis stroke cohort.

Methods

Data were extracted from a prospective cohort comprising all patients presenting to Groote Schuur Hospital (GSH) between 2000 and May 2012 with acute ischaemic stroke, who received thrombolytic therapy with IV tPA according to the GSH Stroke Unit protocol. Patients who received mechanical thrombolysis or intra-arterial tPA were excluded.

Age, gender, past medical history and prior medication were recorded. Admission data of vital signs, serum glucose levels, stroke severity according to the NIHSS, disability according to the modified Rankin score, and details of tPA administration (time to onset and dose) were also recorded. For this study, all available CT brain scans performed on admission (pre-thrombolysis) were re-evaluated by a radiologist in training for signs of early infarct or the dense middle cerebral artery (MCA) sign. The SITS-SICH and SEDAN scores (see below) were calculated from these data and patients were risk-stratified accordingly.

Both the SITS-SICH and SEDAN scoring systems (see Tables 1, 2) were developed using multiple regression analyses, and identified elevated serum glucose levels and high NIHSS scores on admission as poor prognostic indicators. The risk of SICH varied according to the SICH definition used: by the SITS-MOST definition, the risk ranged from 0.2% (score of 0) to 9.2% (score ≥ 9) while the risk of SICH by the ECASS II definition ranged from 1.4% (score 0) to 23.2% (score ≥ 9). The SEDAN score revealed an increasing risk of SICH in the external validation cohort, ranging from 0.01% (score 0) to 27.8% (highest score 6). The single largest risk factor identified for the development of SICH in the SITS-MOST study was dual antiplatelet therapy with both aspirin and clopidogrel.[12,13]

The primary outcome was symptomatic intracranial haemorrhage according to either the SITS-MOST and/or ECASS II definitions. The SITS-MOST definition of SICH is a local or remote type II parenchymal haemorrhage within 22 to 36 hours after treatment (or sooner) associated with a ≥ four-point deterioration on the NIHSS score from baseline or from the lowest score from baseline to 24 hours, or leading to death.[12]

The ECASS II definition of SICH was any intracranial haemorrhage on any post-treatment image, within seven days of initiating treatment associated with a ≥ four-point deterioration on the NIHSS score from baseline or from the lowest score in seven days, or leading to death.[14] Other outcomes reported were death, asymptomatic intracranial haemorrhage (AIH), and extracranial haemorrhage (EH).

During most of the cohort period, the GSH Stroke Unit protocol required post-thrombolysis CT brain scans to be performed routinely within 48 hours of thrombolysis, or urgently with any suspicion of an intracerebral haemorrhage. Post-thrombolysis CT scans were reviewed for this study by a radiologist trainee blinded to clinical outcomes for evidence of intracranial haemorrhage.

Ethical approval was obtained from the UCT Groote Schuur Hospital human research ethics committee (Ref: 499/2013).

Results

In total, 45 patients underwent thrombolysis for acute ischaemic stroke at the GSH Stroke Unit from January 2000 to May 2012. Four patients underwent mechanical thrombolysis with intra-arterial tPA, and were excluded. The remaining 41 patients who received IV tPA for acute ischaemic stroke were included (see Table 3).

Five patients were older than 72 years, and two patients were older than 75 years at stroke onset. Admission systolic blood pressures (SBP) were above 180 mmHg in five patients and greater than 220 mmHg in one patient. Of those taking antiplatelet therapy at the time of admission, all were on aspirin monotherapy. Time to onset of treatment with tPA was greater than 180 min in 13 patients and none of these were treated more than 4.5 hours after onset of symptoms. Pre- and post-thrombolysis CT scans were available for review in 23 patients.

Two patients suffered SICH (ECASS II definition) post-thrombolysis, comprising 4.9% of the cohort. CT scans were available for review in one patient only and confirmed that the haemorrhage fulfilled the SITS-MOST criteria (2.4%). Of the four patients who died during their admission for stroke, one patient suffered a fatal SICH, while three other patients died

Table 1. Components of SITS score and overall risk level[12]

Category	*Points (15)*
Aspirin + clopidogrel therapy	2
Aspirin monotherapy	1
NIHSS > 13	2
NIHSS 7–12	1
Blood glucose ≥ 180 mg/dl*	2
Age ≥ 72 years	1
Systolic BP ≥ 146 mmHg	1
Weight ≥ 95 kg Onset-to-treatment time ≥ 180 min	1
History of hypertension	1

*180 mg/dl ≈10 mmol/l

Table 2. SEDAN score[13]

Category	*Total*	*6*
Blood sugar (glucose) on admission	≤ 8 mmol/l	0
	8.1–12 mmol/l	1
	> 12 mmol/l	2
Signs of early infarction on admission CT*	No	0
	Yes	1
Dense middle cerebral artery sign on admission CT	No	0
	Yes	1
Age (years)	≤ 75	0
	> 75	1
NHSS score on admission	0–9 points	0
	≥ 10 points	1

*Signs of early infarction: hypo-attenuation of the middle cerebral artery territory (< 1/3), obscuration of the lentiform nucleus, cortical sulcal effacement, focal hypo-attenuation, loss of the insular ribbon/obscuration of the Sylvian fissure, loss of grey–white differentiation in the basal ganglia, hypo-attenuation of the basal ganglia.

Table 3. Baseline characteristics

Baseline characteristics (n = 42)	
Median age, years (IQ range)	62 (50–66)
Weight on admission, kg (IQ range)	76 (67–80)
Preceding history of hypertension, *n* (%)	27 (66)
Median systolic BP on admission, mmHg (IQ range)	149 (134–175)
On anti-platelet therapy at admission, *n* (%)	11 (27)
Abnormal serum glucose on admission, *n* (%)	8 (20)
Mean time to thrombolysis (min)	169
Median NIHSS score on admission, *n* (IQ range)	14 (11–17)
CT brain scans (*n* = 23)	
Early signs of infarction, *n* (%)	16 (70)
Hyperdense MCA, *n* (%)	7 (30)

from causes unrelated to thrombolysis therapy: cardiogenic heart failure following an acute myocardial infarction, and recurrent cerebral infarction and subsequent pneumonia. Eight patients had evidence of asymptomatic intracranial haemorrhage, attributed to haemorrhagic conversion of the ischaemic infarct. In four of these patients, the CT scan was available to verify this finding. Two patients had extracranial haemorrhage, including one patient with a hip haematoma.

The median SITS-SICH score for our patient cohort was 4 (IQR 2–5). The patients were stratified into low, average, moderate and high risk (see Table 1). In the GSH cohort, the majority of patients had 3–5 points, or average risk, including the two patients who developed SICH. There were no patients who were scored as high risk (> 9). The distribution of patient risk in the GSH cohort differed from the SITS-SICH cohort, with more patients classified as low or average risk, and no high-risk patients (Table 4).

One GSH patient who had a SEDAN score of 3 suffered a SICH (by both ECASS II and SITS-SICH criteria). There was one death in this group, due to complications related to pneumonia (Table 5).

Discussion

Urgent thrombolysis with IV tPA is a priority in the emergency medical treatment of acute ischaemic stroke. Robust efficacy data exists for this therapeutic modality, particularly when administered within the first 90 min, and the window of benefit has widened since it was first introduced from three to 4.5 hours after onset of symptoms. Published data from the GSH Stroke Unit reveal similar rates of SICH to those from developed and several developing countries, which provide some reassurance to clinicians concerned about the safety profile of this modality in a South African setting. However, the risk of SICH remains, and care should be taken to select patients who are likely to have the most benefit at the lowest risk of SICH.

Table 4. Comparison of SITS-SICH scores and risk of SICH by ECASS II definition for GSH and SITS-MOST validation cohorts

Score	*Total GSH cohort (n = 41) % (n)*	*Total SITS cohort (n = 15 814) % (n)*	*SICH rate (GSH) %*	*SICH rate (SITS) %*
Low (0–2 points)	29 (12 /41)	22.7	0	1.6
Average (3–5 points)	53.7 (22/41)	55	9	4.7
Moderate (6–8 points)	17.1 (7/41)	21.4	0	8.9
High (> 9 points)	0	1.1	0	23.2
Overall rate			4.6 (2/41)	5.1

Table 5. Comparison of SEDAN scores and risk of SICH by ECASS II definition for GSH and SEDAN validation cohorts

Score	*Total GSH cohort (n = 23) % (n)*	*Total SEDAN cohort %*	*SICH rate (GSH) (n = 2) % (n)*	*SICH rate (SEDAN)* %*
0	4.4 (1)	12.4	0	0.9
1	30.4 (7)	27.5	0	3.5
2	34.8 (8)	28.3	0	5.1
3	26.1 (6)	20.9	16.7 (1)	9.2
4	0 (0)	8.6	0	16
5	4.4 (1)	2.2	0	27
6	0	0	0	0

To be practical, the application of risk scores for SICH should include information that is easily obtained in the emergency unit (EU). They should contain independent risk factors for SICH and take into account the interplay between these factors in an individual patient.

The SITS-SICH score uses clinical variables that can be attained relatively quickly and easily at the bedside in a resource-constrained area. It has been validated in over 16 000 patients from multiple centres, many of whom did not have prior experience in thrombolysis. The SEDAN score uses clinical information but it relies on the assessment of brain CT imaging for subtle signs of stroke, which may be overlooked in a busy EU setting by inexperienced reviewers. Many South African centres use older (fewer slice) scanners that would decrease the sensitivity in detecting such signs.

The overall rates of SICH seen in the SITS-SICH validation cohort of 5.1% per ECASS II definition and 1.8% per SITS-MOST definition compare with the GSH rates of 4.8 and 2.4%, respectively. The SICH rate in the SEDAN score validation cohort was 6.5%. There appeared to be a trend towards GSH patients being slightly lower risk than either of the SITS-MOST or SEDAN validation cohorts. This may reflect the more cautious approach in patient selection being used at our centre.

The main limitation of this pilot study was that of small sample size and low event rate in the GSH cohort. One is unable to comment on the ability of either score to reliably predict the risk of haemorrhage. However, the overall rate of SICH by the ECASS II definitions was similar between the cohorts studied.

A further limitation was that CT brain scans taken prior to 2003 were not available for a review of the images, although reports were present. Therefore, signs of early infarction and a dense middle cerebral artery sign could not be evaluated as is required for the SEDAN scoring system, nor could we confirm the presence of a type II parenchymal haemorrhage, required for the SITS-MOST definition of SICH.

Conclusion

The scores, in particular the SITS-SICH score, represent a potentially useful clinical tool to aid in patient selection for thrombolysis in ischaemic stroke. This study, piloting their use in a South African cohort, suggests that they may be applicable in our context but further research is required to validate their use.

With the increasing use of thrombolysis on a national level, such risk-stratification tools might be considered for inclusion into a stroke unit protocol.

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Hypertensive retinopathy and its association with cardiovascular, renal and cerebrovascular morbidity in Congolese patients

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Abstract

Background: Signs indicating hypertensive retinopathy can help determine the extent of hypertensive cardiovascular, renal and cerebrovascular damage.

Objectives: To study the association between hypertensive retinopathy and cardiovascular, renal and cerebrovascular changes, and to determine the predictors of hypertensive retinopathy in Congolese patients.

Methods: A total of 159 hypertensive subjects (mean age: 58.9 ± 13.2 years) were enrolled from the cardiology out-patient clinic. Retinopathy grade was assessed on direct ophthalmoscopy. Hypertensive cardiovascular, renal and cerebrovascular changes were indicated by left ventricular hypertrophy (LVH), chronic kidney disease (CKD) and stroke, respectively.

Results: Hypertensive retinopathy was present in 83.6% of the patients (grade 1: 42.1%; grade 2: 11.3%; grade 3: 23.3%; grade 4: 6.9%). There was no association between hypertensive retinopathy and the presence or absence of LVH (86.5 vs 73.3%, $\chi^2 = 1.53$, $p = 0.21$), chronic kidney disease (89.3 vs 83.3%, $\chi^2 = 0.12$, $p = 0.73$) or stroke (85.7 vs 83.2%, $\chi^2 > 0.001$, $p = 0.99$). On multivariate logistic regression, CKD was the most significant predictor of severe hypertensive retinopathy, with an odds ratio of 4.4.

Conclusion: No association was found between hypertensive retinopathy and LVH, CKD or stroke. CKD was the most significant predictor of hypertensive retinopathy and there was a tendency toward increased risk of target-organ damage among patients with advanced hypertensive retinopathy.

Keywords: hypertension, hypertensive retinopathy, left ventricular hypertrophy, chronic kidney disease, stroke

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Hypertension is a major public health problem worldwide and on the African continent.[1,2] The disease, once considered to be rare outside Europe and North America, is now a leading cause of disability and mortality in developing countries. Its prevalence is projected to reach 30% worldwide by 2025.[2]

Poor control of hypertension increases the likelihood of complications affecting the cardiovascular and cerebrovascular systems, kidney and retina, often labelled under the term target-organ damage (TOD).[1] The development of subclinical TOD, such as left ventricular hypertrophy (LVH), increased intima–media thickness of the large vessels, microalbuminuria following glomerular dysfunction, cognitive decline and hypertensive retinopathy precedes the occurrence of major complications, which include stroke, congestive heart failure and myocardial infarction, renal failure and retinal vascular occlusions.[3-5] In the Democratic Republic of Congo (DRC), the prevalence of systemic hypertension has been reported to be over 25%,[6,7] whereas hypertension and associated complications account for over 20% of deaths among adults.[8]

Studies have demonstrated that TOD increases cardiovascular risks over that already associated with elevated blood pressure alone. For example, it has been shown that once LVH has developed following long-standing systemic hypertension, it behaves as an independent risk factor and a predictor of both further cardiac complications,[9] and other incident vascular events such as ischemic stroke and myocardial infarction.[10] Similarly, the presence of cerebrovascular and renal damage may raise cardiovascular risk over that conferred by hypertension itself.[11,12]

In addition, hypertensive retinopathy has long been known as a predictor of systemic morbidity and mortality. Both epidemiological and clinical studies have provided evidence that markers of hypertensive retinopathy are associated with raised blood pressure, systemic vascular diseases, and subclinical cerebrovascular and cardiovascular disease, and predict incident clinical stroke, congestive heart failure and mortality due to cardiovascular complications.[13] This association of hypertensive retinopathy with other TOD has also been shown to be independent of blood pressure and other risk factors, which supports the recommendation that retinal vascular changes should be assessed in individuals with systemic hypertension for better extra-ocular TOD risk stratification.[13]

While the number of reports on hypertensive TOD has been on the rise on the African continent, the relationship between

hypertensive retinopathy and other TOD has largely remained unexplored. The aim of this study was to examine the association of hypertensive retinopathy with LVH, chronic kidney disease (CKD) and stroke in Congolese patients.

Methods

This cross-sectional, observational study included 159 consecutive Congolese hypertensive patients (73 men, 86 women, mean age 57.9 ± 13.2 years) who were referred from the Cardiology Division to the Ophthalmology Department of the Kinshasa University Hospital for fundus examination as part of a work-up of people with hypertension. All participants provided informed consent and the study was approved by the University of Kinshasa Medical School institutional review board.

Inclusion criteria were age ≥ 18 years, willingness to participate in the study, established diagnosis of hypertension regardless of treatment regimen, duration, severity or aetiology. Exclusion criteria included inaccessibility of the fundus due to media opacities, and pregnancy.

All participants underwent blood pressure measurement with a mercury sphygmomanometer after the patient has been in a sitting position for five minutes, and body mass index (BMI) determination. They provided personal information about history of alcoholism, smoking, as well as family history of hypertension and stroke, and diabetes.

Routine ophthalmological examination was performed, which included measurement of visual acuity, slit-lamp examination of the anterior segment, intra-ocular pressure measurement with applanation tonometry, and ocular fundus assessment with direct ophthalmoscopy after pupil dilation with tropicamide 1% and phenylephrine 10%. The fundus examination specifically looked at retinal abnormalities consistent with hypertensive retinopathy, which was graded based on the Scheie classification:[14] grade 0 = no visible change; grade 1 = barely detectable arterial narrowing; grade 2 = obvious arterial narrowing with focal irregularities; grade 3 = grade 2 plus retinal haemorrhages, exudates, cotton wool spots, or retinal oedema; grade 4: grade 3 plus papilloedema.

Hypertension was defined and classified according to the European Society of Hypertension/European Society of Cardiology guidelines.[15] Data about extra-ocular TOD such as LVH, CKD and stroke were recorded from cardiology medical records. LVH was diagnosed by echocardiogram using ASE criteria:[16] end-systolic left ventricular diameter, septal wall thickness (SWT) and posterior wall thickness were calculated from the two-dimensionnally guided M-mode tracing and measured in five consecutive cardiac cycles. LVH was defined by SWT greater than 11 mm.

CKD was diagnosed according to the Kidney Disease Outcome Quality Initiative (K/DOQI),[17] when glomerular filtration rate (GFR) was lower than 60 ml/min/1.7 m^2 using the equation from the Modified Diet in Renal Disease (MDRD) study.[18] Stroke was diagnosed in the presence of clinical neurological signs consistent with stroke, with or without supporting CT scan lesions.

Statistical analysis

All analyses were performed with SPSS version 15.0 (SPSS, Chicago, IL, USA). Data were expressed as mean ± standard deviation. Student's *t*-test was used to compare means between groups. The proportion of patients with hypertensive retinopathy was compared among those with and without LVH, CKD or stroke using the chi-square test. The chi-square test was also used to compare the proportions of patients with TOD between those with and without hypertensive retinopathy. Multiple logistic regression analysis allowed assessment of the association of demographic and clinical factors including TOD with the likelihood of having hypertensive retinopathy. A $p < 0.05$ was considered statistically significant.

Results

Of the 159 patients included in this study, 73 (46%) were male and 86 (54%) were female, with a mean age of 57.9 ± 13.2 years (range: 19–92). Approximately half of the patients (48.4%) had been hypertensive for one to 10 years; 137 (86.2%) patients had essential hypertension and 22 were diabetic. Hypertension was grade 1 (systolic: 140–159 mmHg and diastolic: 90–99 mmHg), grade 2 (systolic: 160–179 mmHg, diastolic: 100–109 mmHg) and grade 3 (systolic ≥ 180 mmHg, diastolic ≥ 110 mmHg) in 48 (30.2%), 34 (21.4%) and 77 (48.4%) patients, respectively. One hundred and twenty-two (76.7%) patients were on blood pressure-lowering treatment (57.2% had uncontrolled whereas 19.5% has controlled blood pressure) and 37 (23.3%) were not on treatment at the time of study enrolment.

Other characteristics of the study population were as follows: weight 71.8 ± 16.3 kg (range: 42–130), height 163.5 ± 8.9 cm (range: 148–162), waist circumference 90.9 ± 12.8 cm (range: 67–125), systolic blood pressure 159.1 ± 30.9 mmHg (range: 100–230), diastolic blood pressure 95.1 ± 16.6 mmHg (range: 61–157), serum creatinine 2.2 ± 3.6 mg/dl (range: 0.3–19) and blood urea 38.9 ± 42.1 mmol/l (range: 5.2–258).

Hypertensive retinopathy stage 0, 1, 2, 3 and 4 was present in 16.4, 42.1, 11.3, 23.3 and 6.9% of the patients, respectively. Overall, the severity of hypertensive retinopathy increased with increasing systolic and diastolic blood pressures. Data on cardiac state were available for 97 (61%) patients, of whom 52 (53.6%) had LVH. Twenty-eight (31.8%) of the 88 patients who underwent glomerular filtration rate (GFR) assessment had levels consistent with CKD and 28 (17.6%) patients were diagnosed as having stroke.

Table 1 shows the distribution of patients with LVH by stage of retinopathy. The proportions of patients with retinopathy were comparable among those with (86.5%) and without LVH (73.3%) (χ^2 = 1.53, p = 0.21). Similarly, the proportions of patients with LVH did not differ significantly between patients with (57.7%) and those without retinopathy (36.8%) (χ^2 = 0.39, p = 0.53). There was no significant association between hypertensive retinopathy and LVH (χ^2 = 1.9, p = 0.17, OR = 2.3, 95% CI: 0.8–6.6). For all retinopathy stages, the proportions of patients with and without LVH were comparable (p = 0.24–0.99, data not provided in Table 1). The risk of having LVH tended to increase with the severity of hypertensive retinopathy; it was 4.5 times higher for patients with grade 3 hypertensive retinopathy relative to those without retinopathy.

There were 28 patients with CKD; their distribution by retinopathy stage is provided in Table 2. Subgroups of patients with and without retinopathy had similar proportions of patients with CKD (33.3 vs 23.1%) (χ^2 = 0.088, p = 0.77). A similar

Table 1. Association between hypertensive retinopathy and left ventricular hypertrophy (LVH)

Retinopathy grade	*With LVH (%)*	*Without LVH (%)*	*OR (95% CI)*	*Chi-square*	p-*value*
0	7 (13.5)	12 (26.7)	1	–	–
1	19 (36.5)	21 (46.7)	1.6 (0.5–4.8)	0.24	0.62
2	10 (19.2)	5 (11.1)	3.4 (0.8–14.2)	1.91	0.17
3	13 (25.0)	5 (11.1)	4.5 (1.1–17.9)	3.34	0.07
4	3 (5.8)	2 (4.4)	2.6 (0.3–19.3)	0.18	0.67

OR: odd ratio, CI: confidence interval.

Table 3. Association between hypertensive retinopathy and stroke

Retinopathy grade	*With stroke (%)*	*Without stroke (%)*	*OR (95% CI)*	*Chi-square*	p-*value*
0	4 (14.3)	22 (16.8)	1	-	-
1	11 (39.3)	56 (42.7)	1.1 (0.3–3.8)	0.04	0.85
2	6 (21.4)	12 (9.2)	2.8 (0.7–11.7)	1.1	0.30
3	4 (14.3)	33 (25.2)	0.7 (0.2–2.9)	0.02	0.88
4	3 (10.7)	8 (6.1)	2.1 (0.4–11.3)	0.2	0.70

OR: odd ratio, CI: confidence interval.

observation was made regarding the proportions of patients with hypertensive retinopathy among those with and without CKD (89.3 vs 83.3%) ($\chi^2 = 0.12$, $p = 0.73$). The association of CKD with hypertensive retinopathy was not significant for all retinopathy stages combined ($\chi^2 = 0.17$, $p = 0.68$, OR = 1.7, 95% CI: 0.4–6.6) or for each retinopathy stage taken individually ($\chi^2 = 0.03$–2.82, $p = 0.09$–0.85). Compared to patients without hypertensive retinopathy, those with stages 3 and 4 hypertensive retinopathy were 3.3 and 13.3 times more likely to have CKD, respectively.

There were 85.7% of patients with hypertensive retinopathy among those who suffered from stroke (28 patients, Table 3). This proportion was not significantly different from the 83.2% of patients with hypertensive retinopathy among those without stroke ($\chi^2 > 0.001$, $p = 0.99$). Patients with hypertensive retinopathy were as likely as those without retinopathy to have stroke (18 vs 15.4%) ($\chi^2 = 0.34$, $p = 0.56$). No association was found between stroke and hypertensive retinopathy regardless of retinopathy stage ($\chi^2 < 0.01$, $p = 0.96$, OR = 1.2; 95% CI: 0.4–3.8) and for individual retinopathy stages ($\chi^2 = 0.02$–1.06, $p = 0.30$–0.88).

A subset of data of 75 patients with complete documentation was used to perform a multivariate logistic regression analysis that included age, gender, BMI, alcohol consumption, smoking, diabetes, arterial pressures (systolic, diastolic and pulse), current blood pressure-lowering treatment, LVH, CKD and stroke as candidate explanatory variables, and hypertensive retinopathy as outcome variable after controlling for diabetes. The results, shown in Table 4, indicate that CKD was the most significant predictor of hypertensive retinopathy, with OR of 4.4 compared to CKD-free patients. Age > 50 years and smoking appeared to decrease the risk of hypertensive retinopathy; the effects were negligible but significant.

Discussion

Hypertension is an important cause of morbidity and mortality in the general population in Western countries, and recent surveys in sub-Saharan Africa have reported high prevalences of hypertension ranging between 19 and 50% in both urban and rural populations.[19,20] If left untreated, hypertension may result in considerable damage to the cardiovascular, renal and cerebrovascular systems, leading to such complications as myocardial infarction, CKD and cerebrovascular accident.

While significant efforts have been invested to demonstrate the benefits of antihypertensive treatment, it is critical for better management to know both to what extent the various hypertension-related TODs are interrelated, and the risk factors for hypertension-related damage. Because studies in this regard are limited in sub-Saharan Africa, we investigated the relationship between hypertensive retinopathy and LVH, CKD and stroke among Congolese patients. We also assessed the determinants of hypertensive retinopathy.

It has been hypothesised that both hypertension-related retinal and renal vascular changes share common pathogenetic mechanisms. As a result, earlier studies have consistently reported an association between the presence of retinal vascular changes associated with hypertension and lower GFR.[21-23] Surprisingly, our results suggest otherwise, which may be ascribed to the small study population.

Signs of hypertensive retinopathy have also long been recognised as risk indicators of LVH, both in population- and hospital-based studies.[24-26] For example, in the Chronic Renal Insufficiency Cohort (CRIC) study,[26] there was an association between severity of hypertensive retinopathy and the incidence of any cardiovascular disease. Similarly, a follow up of the National Health and Nutrition Survey (NHANES I) reported an increased risk of cardiovascular disease in people with hypertensive ocular fundus retinal vascular changes.[27]

The lack of association between hypertensive retinopathy and LVH found in our study echoes the findings of other earlier studies.[28,29] While there is a general agreement on the association between hypertensive retinopathy and all types of hypertensive cardiovascular diseases,[26,27,30] our study only focused on LVH, which may explain the lack of association. Overall, our findings corroborate those of earlier studies that the risk of developing LVH increases significantly with the severity of hypertensive retinopathy.

Table 2. Association between hypertensive retinopathy and chronic kidney disease (CKD)

Retinopathy grade	*With CKD (%)*	*Without CKD (%)*	*OR (95% CI)*	*Chi-square*	p-*value*
0	3 (10.7)	10 (16.6)	1	–	–
1	9 (32.1)	26 (43.3)	1.2 (0.3–5.2)	0.04	0.85
2	2 (7.1)	13 (21.7)	0.5 (0.07–3.7)	0.03	0.86
3	10 (35.7)	10 (16.7)	3.3 (0.7–15.9)	1.4	0.24
4	4 (14.3)	1 (1.7)	13.3 (1.1–169.1)	2.8	0.09

OR: odd ratio, CI: confidence interval.

Table 4. Significant determinants of hypertensive retinopathy

Parameters	β	p-*value*	*OR (95% CI)*
Constant	–0.88	0.23	0.41
Chronic kidney disease	1.49	0.018	4.4 (1.29–15.21)
Age > 50 years	–1.46	0.046	0.23 (0.06–0.97)
Smoking	–2.02	0.035	0.1 (0.02–0.9)

OR: odd ratio, CI: confidence interval.

In support of Cuspidi *et al.*,[31] the frequency of severe retinopathy (i.e. grade 4) appeared to be low among subjects with LVH. The same observation was made among subjects with CKD as well as those with stroke. While we do not have a definitive explanation for this observation, it is possible that hypertensive patients in our setting have a reduced life expectancy so that severe retinopathy has no time to develop.

Hypertensive retinopathy had no association with stroke in this study, which is at odds with reports from earlier investigations. Indeed, many cross-sectional studies have demonstrated a clear relationship between hypertensive ocular fundoscopic abnormalities and both clinical and subclinical stroke, even after adjusting for other independent vascular risk factors.[32-34] However, definitive convincing evidence in favour of this association has been provided by longitudinal studies.[35-39]

Unlike most of these earlier studies that used ocular fundus photography and brain imaging techniques to increase the diagnostic accuracy, our diagnosis of stroke was clinical and retrospective in nature. As a result, a substantial number of patients who suffered subclinical stroke and/or hypertensive retinopathy, identifiable using imaging techniques, may have been unaccounted for. The cost of medical imaging modalities such as CT scans limits the patient's access to this sensitive diagnostic tool. This limitation is also valid for the association between LVH and hypertensive retinopathy.

Studies on predictors of hypertensive retinopathy have reported conflicting results. For example, while aging, obesity measured by BMI, and smoking have been traditionally associated with increased risk of hypertensive retinopathy, Sharp *et al.*[40] found that age and systolic blood pressure did not influence hypertensive retinopathy in people of African origin, despite a higher prevalence of hypertensive retinopathy in this group compared to people of European descent.

In the ARIC study,[35] only mean blood pressure was associated with hypertensive retinopathy in the subset of participants of African descent. LVH and BMI were not significant determinants, and smoking had a marginally non-significant effect. The risk-reducing effect of aging, smoking, and LVH on retinopathy that we found is surprising and adds to existing inconsistencies in results across studies. We speculated that higher mortality rates, selectively affecting older people as a result of hypertension-related complications, and other morbidities in our setting may contribute to the inverse ORs observed for age and LVH.

Because arteriolar narrowing and arteriovenous nipping can be found in the absence of hypertension, it has been argued that these signs have little or no value in the management of hypertension, and that clear evidence is lacking to show that patients with mild hypertensive retinopathy need physician referral or follow up. Conversely, landmark prospective studies have provided evidence of the clinical value of retinal arteriolar narrowing. For example, in the Beaver Dam Eye study,[41] the five-year incidence of retinopathy in general and that of arteriolar narrowing was significantly higher in patients with elevated blood pressure, despite being on antihypertensive treatment, relative to those with controlled blood pressure and those with no hypertension.

The Blue Mountain Eye study[42] reported an association between generalised retinal arteriolar narrowing at baseline and about a three-fold increased risk of five-year incidents of severe hypertension. These findings emphasise the clinical value of assessing retinal arteriolar change for cardiovascular risk prediction, and are supported by international guidelines for hypertension management such as the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, the European Society of Cardiology, the European Society of Hypertension, and the British Society of Hypertension.

We acknowledge that this study has some limitations. The diagnosis of hypertensive retinopathy, particularly in the early stages, has been shown to suffer from high rates of inter- and intra-observer variability when assessed with direct ophthalmoscopy, as in this study. Because only one observer made the assessment and there was no intra-observer, the results presented herein did not account for the possible effect of low reliability. An additional limitation that may have influenced the results is the small number of study participants who underwent GFR assessment and echocardiogram, which may limit the generalisability of our findings.

Conclusion

There was no association between hypertensive retinopathy and LVH, CKD or stroke in this series. There was a trend towards increased risk for developing TOD among people with advanced retinopathy. CKD emerged as the only significant predictor of hypertensive retinopathy.

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The proposed role of plasma NT pro-brain natriuretic peptide in assessing cardiac remodelling in hypertensive African subjects

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Abstract

Aim: Although plasma NT-proBNP differentiates hypertension (HT) with or without left ventricular hypertrophy (LVH) from hypertensive heart failure (HHF), most of the published data are based on studies in Western populations. Also, most previous studies did not consider left ventricular (LV) diastolic function and right ventricular (RV) function. We therefore examined the relation between NT-proBNP on LV and RV remodelling in an African hypertensive cohort.

Methods: Subjects were subdivided into three groups after echocardiography: hypertensives without LVH (HT) ($n = 83$); hypertensives with LVH (HT+LVH) ($n = 50$); and those with hypertensive heart failure (HHF) ($n = 77$).

Results: Subjects with HHF had significantly higher NT-proBNP levels compared to the HT+LVH group ($p < 0.0002$). NT-proBNP correlated positively with right atrial area, an indirect measure of RV function.

Conclusions: NT-proBNP is proposed as a useful biomarker in differentiating hypertension with or without LVH from hypertensive heart failure in black hypertensive subjects.

Keywords: hypertension, cardiac remodeling, left ventricle, right ventricle, NT-proBNP

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Left ventricular hypertrophy (LVH) represents an important index of pre-clinical disease, and carries incremental prognostic value beyond that afforded by traditional coronary risk factors.[1] In a large cohort of black persons, LVH proved to be an even more powerful predictor of mortality than coronary artery disease and left ventricular ejection fraction (LVEF).[2] Hence early detection of LVH is very important in the management of the hypertensive patient.

Electrocardiography can be very useful in assessing LVH, especially in middle- and low-income countries, because it is relatively cheap, accessible and not much expertise is required to operate an electrocardiography machine. Electrocardiographic criteria for LVH are, however, not very sensitive, while the alternative more accurate method of echocardiography is uneconomical, especially in resource-limited countries.[3] Besides requiring more expertise, the results may not be adequate in all patients, especially in those with obesity or pulmonary disease.[4] This situation has led to research on the use of biomarkers such as NT-proBNP and BNP in the detection of the presence of LVH and monitoring its regression.[5]

B-type natriuretic peptide is a cardiac neurohormone secreted by myocardial cells located on both the atria and ventricles, mainly by LV myocardial cells in response to volume expansion and pressure overload.[6,7] Plasma BNP and NT-proBNP levels are a useful marker of LVH in hypertension, and have also been found to rise progressively with increasing severity of hypertension, particularly when ventricular hypertrophy is present.[6] Similarly, plasma BNP and NT-proBNP levels are useful to discriminate between patients with regard to cardiac remodelling and could be considered as a screening tool to select hypertensive patients eligible for transthoracic echocardiography.[5] NT-proBNP is also a useful biomarker in differentiating hypertensive subjects with LVH from those with heart failure.[8,9]

Most of the current knowledge and published data on the use of plasma NT-proBNP in hypertensive LVH and hypertensive heart failure (HHF) are based on studies in Europe and the United States of America, with a dearth of data in black Africans in whom the burden of hypertension and hypertensive heart disease is very high.[10,11] For example, the THESUS study, which studied 1 006 acute heart-failure subjects in nine sub-Saharan African countries, inclusive of Nigeria, showed that hypertension was the commonest cause of heart failure, accounting for heart failure in 45.4% of cases.[12] In addition, most previous studies on this subject never considered LV diastolic function or RV function, both of which are reported to be prognostic markers in hypertensive heart failure.[13,14] We therefore decided to examine the relationship between circulating NT-proBNP and left and right ventricular remodelling in a black African hypertensive cohort.

Methods

This prospective cohort study was approved by the University of Abuja Teaching Hospital's ethical clearance committee and is in compliance with the Helsinki declaration. The minimum age for participation in the study was 18 years but there was no upper age limit. Recruitment for the present study was initiated in December 2011 and data were obtained until August 2012.

Of the 220 patients with hypertension with or without heart failure enrolled for the study, 10, representing 4.5% of the total enrolment, were excluded because they were diabetic, had regional wall motion abnormality on transthoracic echocardiography, had serum creatinine greater than 170 µmol/l or acute myocardial infarction. Therefore, 210 subjects were studied, of whom 133 were subjects with a new referral for hypertension to the Cardiology Unit, Department of Medicine, University of Abuja Teaching Hospital, and 77 were subjects with hypertensive heart failure, presenting consecutively to the same unit.

Hypertension was defined according the JNC VII guidelines,[15] while heart failure was diagnosed according to the guidelines of the European Society of Cardiology.[16] The functional status of the HF subjects was according to the guidelines of New York Heart Association functional classification.[17] All subjects gave written informed consent to participate in the study.

Each subject had fasting blood sugar level, fasting lipid profile, electrolyte, urea and creatinine levels, and full blood count assessed. Each subject also had blood collected, processed and plasma stored at –80°C until assayed for NT-proBNP. Subjects also had a transthoracic echocardiography performed on the same day that the sample was collected for NT-proBNP assay, the samples being analysed at the Hatter Institute, University of Cape Town.

All the subjects completed a standard questionnaire. Due to the multiplicity of languages in Nigeria, the questionnaire was not translated into any of the local languages. The majority of the subjects were reasonably proficient in the English language. Where there was a need for interpretation, both medical and paramedical staff of the Cardiology Unit of the Department of Medicine of University of Abuja Teaching Hospital assisted.

The questionnaire requested specific answers to date of birth, gender, occupation, background diagnosis of hypertension, background diagnosis of diabetes mellitus, history of angina pains, history of alcohol consumption and history of smoking habits. Details of anthropometric measurements, conventional blood measurements and assays for NT-proBNP have been reported in our previous publication.[18]

Echocardiography was performed using a commercially available ultrasound system (Vivid E). Subjects were examined in the left lateral decubitus position using standard parasternal, short-axis and apical views. Studies were performed by an experienced echocardiographer according to the recommendations of the American Society of Echocardiography[19].

In our echocardiography laboratory, the intra-observer concordance correlation coefficient among the three cardiologists involved in the study ranged from 0.76–0.93, while that of the inter-observer concordance ranged from 0.82–0.95. Measurements were averaged over three cardiac cycles. The left and right atrial areas were measured at end-ventricular systole when the atrial chambers were at their greatest dimension, and with the bases of both atria at their greatest dimensions. Other details of our echocardiography measurements have been reported in our previous publication.[18]

Statistical analysis

SPSS software version 16.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. Continuous variables were expressed as mean ± SD. Comparison of demographic, clinical, laboratory and echocardiographic parameters among the three groups was performed by ANOVA test of variance. Correlation coefficients were calculated by linear regression analysis with serum NT-proBNP log-transformed to establish normality, and correlations between serum NT-proBNP and continuous demographic, clinical, laboratory and echocardiographic data were evaluated with Spearman's regression.

Multivariate linear regression analyses were performed with log-transformed NT-proBNP concentrations as dependent variable, with the inclusion of demographic, clinical, laboratory and echocardiographic parameters. A two-tailed p-value < 0.05 was considered significant

Results

Table 1 shows the demographic, clinical and laboratory characteristics of the subjects studied. Subjects with hypertensive HF had the lowest weight of the three study groups, with a body mass index of 25.4 ± 4.5 kg/m^2 as against 27.6 ± 6.6 kg/m^2 for subjects with hypertension with or without LVH (p = 0.03). Hypertensive subjects with LVH had the highest levels of mean arterial pressure and pulse pressure, while subjects with hypertensive HF had the lowest levels.

There was no significant difference among the study populations in the levels of fasting blood sugar, fasting lipid profile, urea, creatinine, haemoglobin concentration and white blood cell count. There was also no significant difference in the NT-proBNP levels between the hypertensive subjects without and those with LVH.

Fig. 1 shows the different concentrations of plasma NT-proBNP in the hypertensive cohort. Subjects with hypertensive HF had significantly higher NT-proBNP levels when compared with other hypertensive subjects, whether with or without LVH ($p < 0.001$).

Table 2 shows the echocardiographic characteristics of all the subjects studied. Hypertensive subjects with LVH had significantly higher interventricular and left ventricular posterior wall hypertrophy when compared with hypertensive subjects without LVH ($p < 0.001$ and 0.001, respectively), and when compared with subjects with hypertensive HF ($p < 0.001$). Hypertensive subjects with LVH also had higher LV mass and LV mass index when compared with hypertensive subjects without LVH and HF ($p < 0.001$). They had a smaller LV mass, whether indexed or not, when compared with hypertensive HF subjects ($p < 0.001$).

Hypertensive subjects without LVH and left ventricular HF had the highest LV ejection fraction ($p < 0.02$) when compared with hypertensive subjects with LVH, and when compared with subjects with HF ($p < 0.001$). Apart from the right atrial area, hypertensive HF subjects had significantly higher chamber diameters. They also had the highest mitral E/A ratio and the lowest tricuspid annular plane systolic excursion value.

Table 1. Clinical profile of the subjects

Parameters	*All* (n = *77*)	*Male* (n = *54*)	*Female* (n = *23*)	p-*value*
Age, years	53.8 ± 13.2	53.8 ± 15.8	51.7 ± 13.6	0.56
Smoking habits, *n* (%)	24 (13.1)	22 (18.6)	2 (2.5)	< 0.001
Body mass index, kg/m²	24.30 ± 7.0	24.2 ± 7.6	24.5 ± 5.9	0.86
Palpitations, *n* (%)	40 (51.9)	24 (44.4)	16 (69.6)	0.002
Peripheral oedema, *n* (%)	49 (63.2)	35 (64.8)	14 (60.8)	NS
NYHA class				
II, *n* (%)	14 (18.2)	10 (18.5)	4 (17.5)	
III, *n* (%)	49 (63.6)	35 (64.8)	14 (60.8)	
IV, *n* (%)	14 (18.2)	9 (16.7)	5 (21.7)	
SBP, mmHg	149.1 ± 23.8	149.9 ± 23.8	147.7 ± 23.9	0.55
DBP, mmHg	98.1 ± 13.9	98.2 ± 13.9	97.9 ± 13.9	0.92
PP, mmHg	55.8 ± 16.2	56.4 ± 16.8	54.7 ± 15.0	0.52
MAP, mmHg	101.3 ± 16.4	101.2 ± 17.2	101.5 ± 15.0	0.89
FBS, mmol/l	5.3 ± 2.2	5.2 ± 2.0	5.4 ± 2.4	0.58
Total cholesterol, mmol/l	4.2 ± 1.2	4.1 ± 0.2	4.3 ± 1.2	0.22
LDL cholesterol, mmol/l	2.7 ± 0.9	2.6 ± 1.0	2.8 ± 1.0	0.14
HDL cholesterol, mmol/l	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.3	0.63
Estimated GFR, ml/min/1.73 m²	101.5 ± 38.8	111.6 ± 41.4	78.3 ± 17.0	< 0.0001
NT-proBNP, pg/ml	501.7 ± 199.8	513.0 ± 208.5	478.7 ± 184.7	0.58
Serum ST2, ng/ml	112.9 ± 78.7	100.1 ± 60.4	134.4 ± 98.3	0.26

SBP = systolic blood pressure, DBP = diastolic blood pressure, PP = pulse pressure, MAP = mean arterial pressure, FBS = fasting blood sugar, LDL = low-density lipoprotein, HDL = high-density lipoprotein, GFR = glomerular filtration rate.

Table 2. Echocardiographic profile of the subjects

Parameters	*All* (n = *77*)	*Male* (n = *54*)	*Female* (n = *22*)	p-*value*
RVD, cm	3.4 ± 0.6	3.5 ± 0.6	3.2 ± 0.5	0.22
Left atrial diameter, cm	4.6 ± 0.9	4.6 ± 0.9	4.5 ± 0.8	0.17
IVSDd, cm	1.1 ± 0.3	1.1 ± 0.2	1.0 ± 0.3	0.03
PWDd, cm	1.1 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	0.07
EDD, cm	5.8 ± 1.1	5.9 ± 1.1	5.5 ± 1.1	0.04
ESD, cm	4.7 ± 1.3	4.9 ± 1.2	4.5 ± 1.3	0.07
LAA, cm²	24.5 ± 7.0	24.5 ± 6.7	24.4 ± 7.5	0.95
RAA, cm²	22.3 ± 8.1	22.6 ± 8.0	21.7 ± 8.5	0.50
LVM/height$^{2.7}$	108.3 ± 46.3	117.5 ± 35.4	112.5 ± 42.3	0.65
LVEF, %	35.2 ± 17.5	34.4 ± 16.8	36.6 ± 18.7	0.58
ME, m/s	0.78 ± 0.3	0.76 ± 0.30	0.81 ± 0.30	0.43
MA, m/s	0.49 ± 0.2	0.49 ± 0.2	0.49 ± 0.1	0.25
ME/MA	2.2 ± 1.3	2.0 ± 1.2	2.2 ± 1.4	0.96
DT, ms	143.2 ± 80.6	143.7 ± 85.1	142.2 ± 72.2	0.22
TAPSE, mm	16.2 ± 5.1	16.6 ± 5.4	15.5 ± 4.5	0.16
TAPSE < 15 mm (%)	33 (42.9)	54 (40.7)	10 (41.7)	0.18
RVSP, mmHg	31.4 ± 10.5	31.4 ± 10.4	31.3 ± 10.5	0.97

RVD = right ventricular diameter in diastole, IVSDd = interventricular septal diameter in diastole, PWDd = posterior wall diameter in diastole, EDD = end-diastolic diameter, ESD = end-systolic diameter, LAA = left atrial area, RAA = right atrial area, LVM = left ventricular mass, LVEF = left ventricular ejection fraction, ME = early mitral inflow, MA = late mitral inflow, DT = deceleration time, TAPSE = tricuspid annular plane systolic excursion, RVSP = right ventricular systolic pressure.

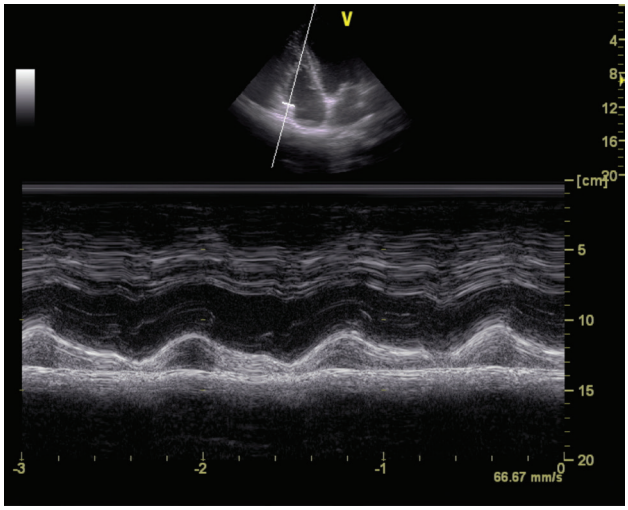

Fig. 1. Top: apical four-chamber view of one of the subjects with the M-mode cursor at the tricuspid annulus. Bottom: M-mode image of the tricuspid annulus from where TAPSE is measured.

Table 3. Clinical and echocardiographic correlates of NT-pro BNP

Parameters	*Coefficient of association* (r)	p-*value*
Age (years)	0.17	0.04*
BMI	–0.07	0.40
Pulse pressure	0.26	0.002*
Mean arterial pressure	0.26	0.002*
IVSDd	0.17	0.05
PWDd	0.08	0.36
LVIDd	0.16	0.05
LVIDs	0.21	0.01*
RVD	0.09	0.31
LAA	0.02	0.80
RAA	0.20	0.04*
LVM/height$^{2.7}$	0.09	0.30
LVEF	–0.21	0.01*
ME	0.02	0.79
MA	0.12	0.15
Mitral E/A ratio	0.08	0.35
Deceleration time	0.14	0.09
TAPSE	–0.23	0.15

IVSDd = interventricular septal diameter in diastole, PWDd = posterior wall diameter in diastole, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, RVD = right ventricular diameter in diastole, LAA = left atrial area, RAA = right atrial area, LVM = left ventricular mass, EF = ejection fraction, ME = early mitral inflow, MA = atrial or late mitral inflow, TAPSE = tricuspid annular plane systolic excursion.
*Significant at $p < 0.05$.

Table 4. Univariate analysis with right ventricular systolic pressure and cardiac biomarkers

Parameters	*Pearson correlation*	p-*value*
Serum ST2	0.75	< 0.0001
NT-proBNP	0.54	< 0.0001

Pearson correlation analysis of clinical and echocardiographic variables with log-transformed NT-proBNP in the study population is shown in Table 3. NT-proBNP was significantly associated with left ventricular ejection fraction ($p = 0.01$) but not with tricuspid annular pulmonary systolic excursion (TAPSE). It was also significantly correlated with age ($p < 0.04$), pulse pressure and mean arterial pressure ($p = 0.002$ and $p = 0.002$, respectively), systolic blood pressure ($p = 0.007$), serum creatinine level ($p = 0.038$) and right atrial area ($p < 0.0001$). There was no significant correlation between NT-proBNP and body mass index, right ventricular diameter in diastole, interventricular septal wall thickness in diastole, posterior wall diameter in diastole, left atrial area, LV mass index, transmitral E/A ratio, deceleration time and TAPSE.

In multivariate linear regression analysis (Table 4), independent predictors of NT-proBNP in the study population included LV ejection fraction ($t = 2.11$; $p = 0.037$), right atrial area ($t = 1.99$; $p = 0.048$) and LV internal diameter in systole ($t = 2.21$; $p = 0.029$).

Discussion

This study has shown that NT-proBNP differentiates hypertensive LVH from hypertensive HF not only in Caucasians,[9] but also in black African hypertensive subjects. We found no significant difference in the concentrations of NT-proBNP between hypertensive subjects with LVH and those without LVH, which is in keeping with previous findings.[5,24,25] NT-proBNP concentrations were not correlated with LV mass index, interventricular septal wall thickness or posterior wall thickness in diastole, which is similar to other findings.[9] This lack of correlation between NT-proBNP and LV mass index might explain why NT-proBNP is not a good marker for differentiating hypertensive LVH from hypertension without LVH and HF.

NT-proBNP correlated with both mean arterial pressure and pulse pressure. Age and plasma creatinine levels were found to correlate with NT-proBNP concentration in our study, in keeping with previous reports that NT-proBNP rises with increasing age,[26,27] and worsening renal status.[28]

Similar to previous findings, we showed no correlation with deceleration time and trans-mitral E/A ratio, which are indices of left ventricular function. Richard *et al*.,[31] however, found a relationship between LV diastolic function and plasma BNP levels using newer diastolic indexes measured from tissue Doppler imaging and colour M-mode that allow more accurate characterisation of myocardial relaxation and left ventricular filling.

Unlike some previous studies, our study did not only assess remodelling of the left-sided chambers and LV systolic function, but also remodelling of the right heart chambers, LV diastolic function and right ventricular systolic function.

Even though there was no significant correlation between the concentration of NT-proBNP and TAPSE, the right atrial area, which is a measure of remodelling of the right cardiac chamber and an indirect measure of right ventricular function, correlated significantly with NT-proBNP. This suggests right cardiac chamber remodelling had some effect on the concentration of plasma NT-proBNP in our hypertensive cohort. Correlation between BNP and right atrial size has been previously described.[32,33]

Hypertensive subjects with LVH had significantly worse LV systolic function compared to subjects without LVH ($p < 0.02$), which may support the fact that hypertensive subjects with LVH have worse cardiovascular profile compared to those without hypertrophy.[34]

Our subjects with hypertensive HF were much younger, with a mean age of 53.0 ± 11.9 years compared to the developed countries where HF is a disease of the elderly, with an average age of 76 years.[35,36] Hypertensive HF presenting in a relatively young cohort in this Nigerian population is a reflection of the presentation of the complications of hypertension at an early stage.

Long distance and often lack of funding to cover the travel fare are important aspects of late presentation to healthcare.[37] This presentation of hypertensive HF at a relatively early age has the potential to undermine national productivity as a consequence of the number of active life years lost by the most active workforce of the population.

Conclusion

This study has shown that NT-proBNP is a good marker in differentiating hypertensive HF from hypertension with or without LVH. Our finding supports the need to introduce NT-proBNP point-of-care machines[39] in our cardiology practices in sub-Saharan Africa. Currently, the use of point-of-care tests in resource-limited settings such as ours has focused mainly on infectious diseases that need prompt diagnosis and treatment, such as HIV infection, tuberculosis and malaria,[40] and diabetes care.[41]

Therefore the need for the introduction of point-of-care NT-proBNP assays for early diagnosis while awaiting echocardiography in our cardiology practice cannot be over-emphasised. For such a point-of-care test to be very effective in the sub-continent, there is a need to further reduce the cost of these devices compared with what is obtainable in Europe and the United States.

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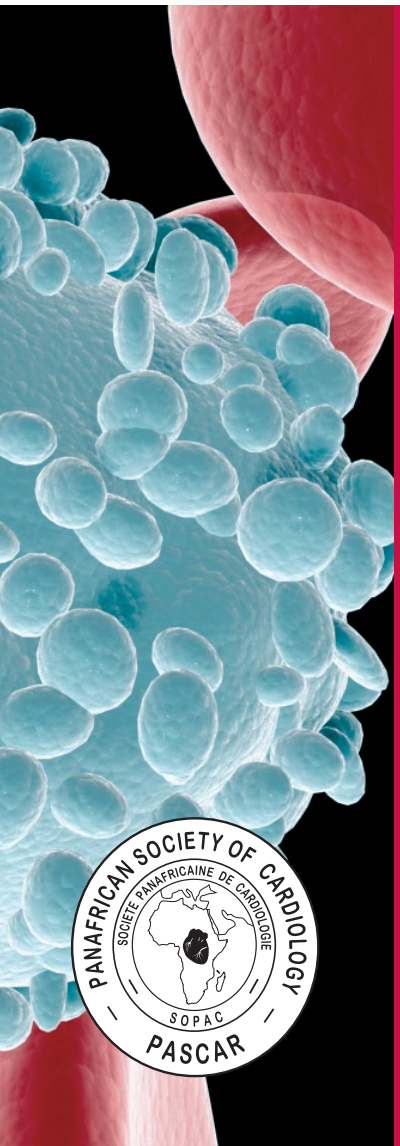

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Troubleshooting techniques for the Endurant™ device in endovascular aortic aneurysm repair

George S Georgiadis, George A Antoniou, George Trellopoulos, Efstratios I Georgakarakos, Christos Argyriou, Miltos K Lazarides

Abstract

Endovascular aortic aneurysm repair with the Endurant™ stent-graft system has been shown to be safe and effective in high-risk surgical patients with complex suprarenal and/or infrarenal abdominal aortic aneurysm anatomy. The wire-formed M-shaped stent architecture and proximal springs with anchoring pins theoretically permit optimal sealing in shorter and more angulated proximal aneurysm necks even under off-label conditions. Nonetheless, extremely difficult anatomical situations and inherent graft system-related limitations must be anticipated. Herein, we describe our techniques to overcome the capture of the tip sleeve within the suprarenal bare-stent anchoring pins, other endograft segments, and native vessels.

Keywords: abdominal aortic aneurysm, endovascular aortic aneurysm repair, stent-graft, Endurant device, techniques

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Previous randomised trials have confirmed the short and mid-term benefits of endovascular abdominal aortic aneurysm repair versus open repair.[1,2] However, its success is dependent on specific anatomical parameters that include the abdominal aortic aneurysm (AAA) morphology and dimensions. Adverse anatomical characteristics such as very short and severely angulated proximal aortic necks or small and tortuous iliac arteries can occasionally preclude its use. Advances in AAA endograft device technology have significantly contributed to improved patient outcomes, and durability of the procedure allows for a wider therapeutic spectrum of patients to receive endovascular repair (EVAR).

The success of these new stent-graft devices results from better adaptation and improved performances in challenging anatomies and better trackability of delivery systems.[3-8] Specific advancements include improved tip design and greater flexibility, controlled proximal stent-graft release mechanism with re-positional proximal stent-graft capabilities, and improved deliverability and placement accuracy.[3-9] These technological advances, combined with cumulative physician clinical experience and enhanced skill sets, have resulted in the consideration of endoluminal grafting in off-label conditions.

A recent report highlighted the application of troubleshooting techniques to overcome 'pitfalls' in some of the steps of EVAR with the Endurant™ (Medtronic Cardiovascular, Santa Rosa, CA) stent-graft device.[10] Herein, we specifically describe simple techniques to overcome capture of the Endurant™ tip sleeve within the suprarenal bare-stent anchoring pins or within other endograft and native vessel segments, in order to avoid emergency conversion to open repair and the potential for adverse outcomes.

The Endurant™ stent-graft system

This stent-graft is a new fourth-generation device comprising a high-density multifilament polyester graft material of low porosity, externally supported by an electropolished nitinol stent structure and loaded in a low-profile hydrophilic coating delivery system. The seals of the European Union (EU) as well as Food and Drug Administration (FDA) approval for this device were received in July 2008 and December 2010, respectively.

The Endurant™ stent-graft is designed to enhance performance in AAA patients with straightforward (friendly) or challenging (hostile) anatomies. Its high flexibility and conformability enables the device to adapt to straight as well as severely tortuous proximal aortic necks and challenging iliac artery anatomies. These stent-grafts have a sinusoidal M-shaped architecture with a small amplitude providing optimal sealing in short and angulated proximal aneurysm necks. Furthermore, the M-shaped proximal stent at the upper pole of the endograft body facilitates enhanced wall apposition, minimising the risk of in-folding and providing another 5 mm of sealing zone.

The Endurant™ stent-graft relies on proximal active fixation, incorporating a suprarenal bare stent ring with anchoring pins of increased flexibility, compared to earlier generation stent-grafts. Initially covered by the tip sleeve, the suprarenal stent with anchoring pins provides controlled release and secure fixation. The radiopaque markers at the proximal and distal edges of the stent-graft as well as the flow divider and contralateral gate markers ensure accurate positioning of the device. Apart from a more flexible main body, the limb stent and optimal stent spacing offer

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more distal longitudinal flexibility and are designed to prevent kinking and provide refined adaptation to tortuous iliac arteries.

Finally, the graft delivery system is reduced by approximately 3 French (Fr) sizes from the smallest prior endograft delivery system. It is available in outer diameters from 18- to 20-Fr for the main body and from 14- to 16-Fr for the extensions. Bifurcated main body proximal diameters include sizes of 23, 25, 28, 32 and 36 mm; limb diameters include sizes of 10, 13, 16, 20, 24 and 28 mm. The diameter of the stent-graft is oversized by approximately 20% in relation to the outer aortic diameter at the proximal fixation zone and about 10% in the distal landing zones (usually the common iliac arteries).

Recently, renovation of the Endurant™ system has resulted in an improved version. Endurant® II provides three additional advanced design features: (1) a 35% extended hydrophilic coating allows the 28-mm-diameter bifurcated component to fit inside an 18-Fr outer diameter catheter (initially 20-Fr with the original Endurant); (2) availability of two new contralateral limb lengths (156 and 199 mm) enables more configuration options and requires fewer total components; and (3) improved radiopacity of the distal end of the bifurcated component's contralateral gate increases visibility. The Endurant® II device received FDA approval in June 2012.[11] The following technical scenarios are also applicable to Endurant® II.

Technical notes

Scenario 1: Capture of the tip sleeve within the suprarenal bare-stent anchoring pins

This scenario assumes that the main body of the bifurcated component of the Endurant™ stent-graft is deployed and the delivery system advanced proximally as far as 3 cm apart from the suprarenal stent [see manufacture instructions for use (IFU) for system details]. The next step is very crucial and failure to withdraw the delivery system until the spindle is retracted into the fabric portion of the stent-graft results in trapping of a suprarenal crown within the tapered tip sleeve.

Even though the steps described in the IFU for the Endurant™ stent-graft system may be followed accurtely, in some cases, especially severe angulated necks (≥ 60°), the markedly flexible delivery system will follow the aortic configuration and stack within the hooks of the suprarenal stent. To avoid the need for open conversion, three simple techniques to successfully remove the delivery system of this endograft are described:

- The first action is to completely remove the stiff or super-stiff guide wire (usually Amplatz™, Ontract, Archer™ or Lunderquist) inside the delivery system, and then rotationally withdraw the delivery system. Removing the wire allows the graft to follow the natural aortic anatomy. Under straightforward circumstances, the device may bend along the body–ipsilateral endograft, possibly avoiding stacking at the level of the anchoring pins.
- The above manoeuvre might be performed more safely if catheterisation of the docking limb and insertion and deployment of the contralateral limb precedes delivery system withdrawal. Otherwise its removal may be facilitated by keeping the contralateral limb in place while moderately inflating (less than the suprarenal aortic diameter) the molding balloon (e.g. Reliant®, Equalizer or Coda) at the pins' level prior to downward removal of the delivery system (Fig. 1A, 1B).
- When compelling anatomical conditions exist, another option is to place a large introducer sheath (e.g. Cook 16- or 24-Fr), through the already catheterised docking limb, advancing above the suprarenal stent before delivery system withdrawal. This manoeuvre leads to aorto-iliac axis 'technical remodelling' with further proximal neck straightening, a condition

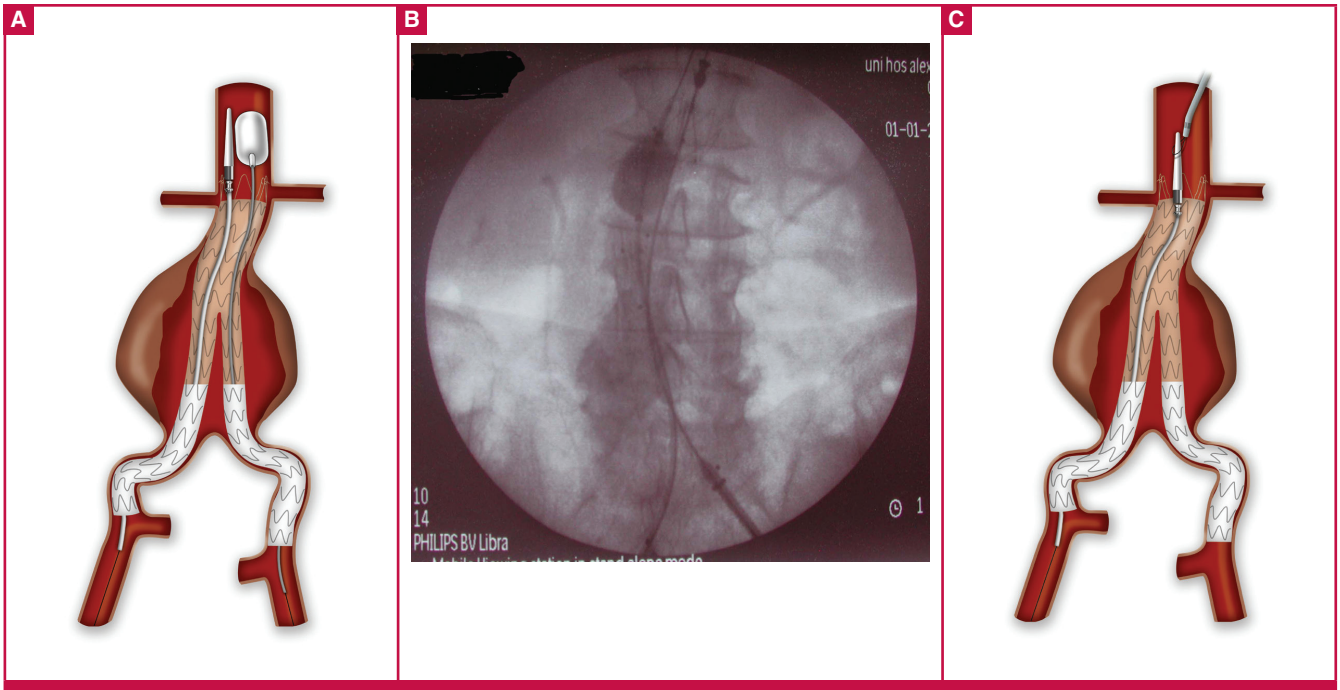

Fig. 1. (A) Inflation of the moulding balloon at the level of the pins prior to downward removal of the delivery system. (B) Angiogram showing the above manoeuvre. Note the balloon that pushes the delivery system in the opposite direction. (C) Use of a snare device to capture the spindle, while simultaneously retracting the delivery system with slow rotational movements.

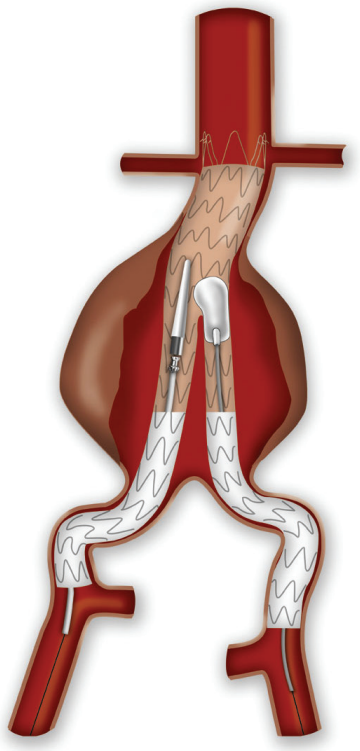

Fig. 2. The balloon pushes the delivery system to the ipsilateral endograft wall when the latter is retracted slowly.

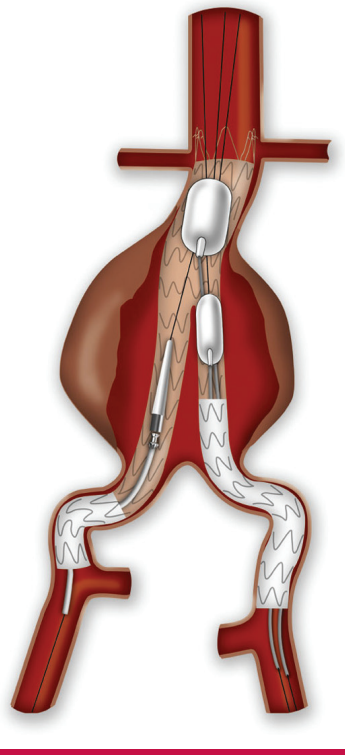

Fig. 3. The balloons are simultaneously dilated and kept in a constant position, thus stabilising the endograft while the delivery system is withdrawn from the ipsilateral limb.

that may help to alter the path that the system follows when rotated downwards for removal. The proximal neck might also be straightened after placing a super-stiff or extra-stiff guide wire from the left brachial artery and through the endograft to exit from the contralateral femoral side.

- The last option replaces the guide wire with a snare device that is introduced through a 7-, 12- or 14-Fr sheath via the left brachial artery access, and captures the spindle while simultaneously retracting the delivery system with slow rotational movements (Fig. 1C).

Scenario 2: The delivery system blocks at the flow divider level

In this situation the delivery system moved slightly upwards. The troubleshooting technique includes first deployment of the contralateral limb in the standard fashion, followed by insertion of a moulding balloon (e.g. Reliant®, Equalizer or Coda), which is inflated in the same manner as required to push the delivery system to the ipsilateral endograft wall, when the latter is retracted slowly (Fig. 2).

Scenario 3: The delivery system blocks at the ipsilateral limb

Two moulding balloons (e.g. Reliant®, Equalizer or Coda) are required in this situation. They are inserted through a 14-Fr Cook introducer sheath from the contralateral site after the contralateral limb is completely liberated and dilated. One moulding balloon is positioned above the flow divider and the second one at the body-to-contalateral limb overlapping area. They are simultaneously dilated and kept in a constant position, thus stabilising the endograft while the delivery system is withdrawn from the ipsilateral limb (Fig. 3).

The same concept may be applied with a larger balloon coming from above through the left brachial artery. In this case the balloons are inflated and retracted in opposite directions. This bidirectional balloon retraction allows more powerful downward movement of the delivery system.

Scenario 4: The delivery system blocks at the external iliac artery

The only way to avoid open conversion in this scenario is to perform a balloon angioplasty of the external iliac artery. Catheterise the delivery system, insert a second 180-cm (0.035-inch) hydrophilic wire between the delivery system and the arterial wall, and place it into the aneurysm sac (Fig. 4A, 4B). A small-diameter (4–6 mm) balloon is introduced over the wire and then into the external iliac artery. Under low pressure, angioplasty is performed. It is not required to fully dilate the balloon up to 8 Atm since the purpose is just to freely remove the delivery system from the stenotic area. In this scenario not only a guide wire, but even a sheath and later a balloon, can be inserted through the delivery system.

Discussion

Improvements in the endovascular stent-graft design, device delivery and deployment characteristics have all resulted in

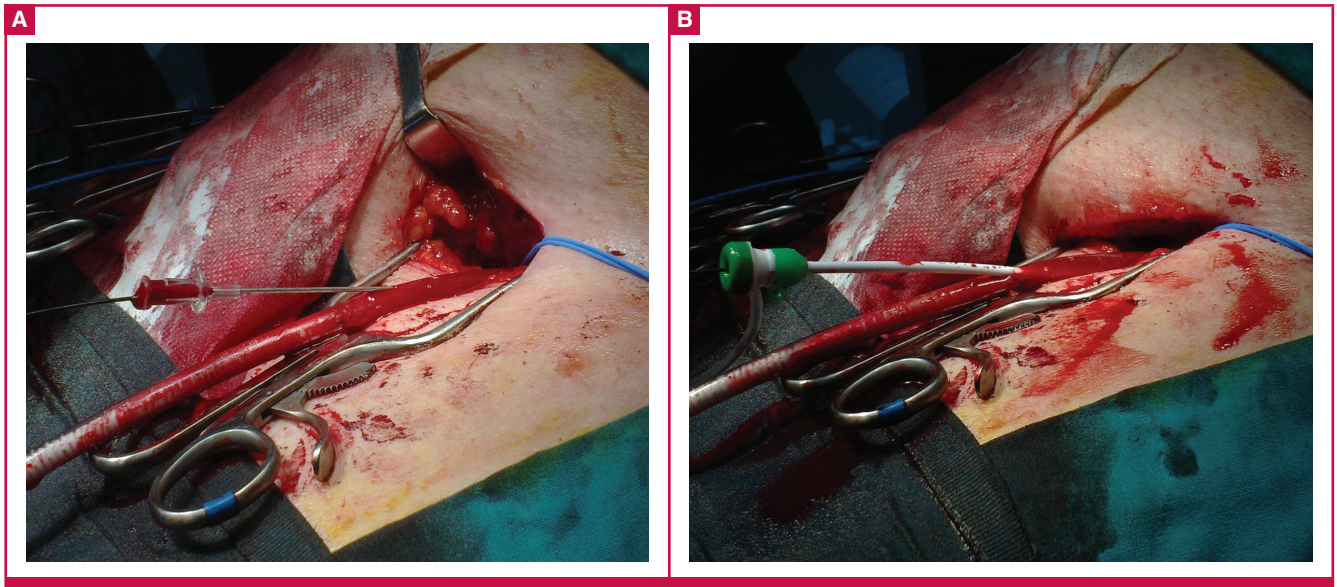

Fig. 4. Catheterisation of the delivery system in order to insert the small-diameter (4–6 mm) balloon into the external iliac artery. Initially a guide wire is inserted through the delivery system (A), and then a short sheath (B). The next step (not shown) is the insertion of the balloon through the sheath.

increased use of EVAR for not only straightforward cases but for those with more complex and challenging aneurysm anatomies. The tips and tricks presented in this report regarding Endurant™ trapped delivery systems should prove especially useful for procedures involving adverse proximal aortic necks and iliac anatomies. It is important to remember that hostile infrarenal aortic aneurysm anatomy such as a very short, severely angulated or dilated proximal neck still remains a major cause of early failure of EVAR and jeopardises long-term efficacy.

Introduction of new endograft devices into the vascular realm will most likely expand the indications for procedures once considered not feasible in the past. Anatomical morphology and measurements of the aneurysm will be crucial to device selection, and device choice critical to the successful positioning and adaptation of the stent-graft to the aneurysm environment for its exclusion from the circulation.

The Endurant™ stent-graft is part of a next-generation system that was designed with the clear intention of expanding the applicability of EVAR for AAA. Initial clinical experience has demonstrated that it can be used in challenging anatomies and can be delivered and deployed safely, even in highly angulated (> 60°) and short (< 15 mm) proximal necks.[5,6] Moreover, accruing experience suggests its safety, even in compelling off-label indications.[7,10,12] Despite the fact that durable efficacy of EVAR using the Endurant™ device remains to be demonstrated, intra-operative performance of this endograft in hostile aneurysm morphology adds valuable information to other recently reported clinical short- and mid-term results.[5-8,10,12]

Technical manoeuvres may occasionally be required in difficult anatomies in order to avoid severe complications. Although not confirmed in all Endurant clinical studies,[12] one problem reported in short and tightly angulated necks is the difficulty of retrieving the conical proximal shelter for the non-covered proximal stent.

In a recent study, comparing the performance of the newly released Edurant II® endograft in patients with friendly and hostile infrarenal aortic anatomy eligible for EVAR, the necessity of troubleshooting techniques was significantly higher in the hostile group.[10] Herein, we described some of these techniques, including those most frequently encountered, the capture of the tip sleeve within the suprarenal bare-stent anchoring pins.[10]

Its easy, accurate and controlled deployment, coupled with its unique high flexibility and conformability contributes to its successful use, even in severely angulated proximal necks and/or iliac arteries. Friendly and hostile groups had equal performance regarding all primary outcome measures, suggesting that expanded EVAR indications can be applied with this stent-graft.[10] Knowledge of these described troubleshooting techniques should allow physicians to handle even the most extreme scenarios with the Endurant™ endograft system and other endoprostheses featuring a suprarenal stent with anchors or pins.

Conclusion

The tips and tricks presented in this report should prevent or reduce conversion to an open procedure when the Endurant™ delivery system becomes trapped in the suprarenal stent anchoring pins or other graft segments. While this report is written specifically for the Endurant™ device system, lessons gleaned are applicable to similar endograft systems.

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New culprit identified in metabolic syndrome

A new study suggests uric acid may play a role in causing the metabolic syndrome, a cluster of risk factors that increases the risk of heart disease and type 2 diabetes.

Uric acid is a normal waste product that is removed from the body by the kidneys and intestines and is released in the urine and stools. Elevated levels of uric acid are known to cause gout, an accumulation of the acid in the joints. High levels are also associated with markers of the metabolic syndrome, which is characterised by obesity, high blood pressure, and elevated blood sugar and cholesterol levels. But it has been unclear whether uric acid itself is causing the damage or it is simply a by-product of other processes that lead to the dysfunctional metabolism.

New research from the Washington University suggests that excess uric acid in the blood is no innocent bystander. Rather, it appears to be a culprit in disrupting normal metabolism. The research team states that uric acid may play a direct, causative role in the development of the metabolic syndrome. The work showed that the gut is an important clearance mechanism for uric acid, opening the door to new potential therapies for preventing or treating type 2 diabetes and the metabolic syndrome.

Recent research by the senior author, Kelle H Moley, the James P Crane professor of obstetrics and gynecology, and her collaborators has shown that a protein called GLUT9 is an important transporter of uric acid. The team studied mice to learn what happens when GLUT9 stops working in the gut, essentially blocking the body's ability to remove uric acid from the intestine. In this study, the kidney's ability to remove uric acid remained normal.

Eating regularly, mice missing GLUT9 only in the gut quickly developed elevated uric acid in the blood and urine compared with control mice. And at only six to eight weeks of age, they developed the hallmarks of the metabolic syndrome: high blood pressure, elevated cholesterol and blood insulin levels, and fatty liver deposits, among other symptoms.

The researchers also found that the drug allopurinol, which reduces uric acid production in the body and has long been used to treat gout, improved some but not all of the measures of metabolic health. Treatment with the drug lowered blood pressure and total cholesterol levels.

Exposure to uric acid is impossible to avoid because it is a normal byproduct of cell turnover in the body. But there is evidence that diet may contribute to uric acid levels. Many foods contain compounds called purines that break down into uric acid. Adding to growing concerns about fructose in the diet, evidence suggests that fructose metabolism in the liver also drives uric acid production.

Switching to foods heavy-laden with fructose over the past 30 years has been devastating, according to Moley. 'There's a growing feeling that uric acid is a cause, not a consequence, of the metabolic syndrome. The medical community now knows that fructose directly makes uric acid in the liver. With that in mind, the laboratory is doing further research to study what happens to these mice on a high-fructose diet.'

Source

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How to approach aortic valve disease in the elderly: a 25-year retrospective study

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Abstract

Objective: In the last decade, the number of elderly patients suffering from aortic valve disease has significantly increased. This study aimed to identify possible factors that could affect surgical and long-term outcomes in the light of a literature review regarding the management of aortic valve disease in the elderly.

Methods: Between January 1990 and December 2012, a total of 114 patients (64 males, 50 females; mean age 76.6 ± 3.6 years; range 70–87 years) with aortic valve replacement (AVR) alone, or combined with coronary artery bypass grafting (CABG) or mitral surgery in our hospital, were retrospectively analysed.

Results: In-hospital mortality was seen in 19 patients. The major causes of in-hospital mortality were low-cardiac output syndrome in eight patients (42.1%), respiratory insufficiency or infection in six (31.5%), multi-organ failure in four (21%), and stroke in one patient (5.2%). The main postoperative complications included arrhythmia in 26 patients (22.8%), renal failure in 11 (9.6%), respiratory infection in nine (7.9%), and stroke in three patients (2.6%). The mean length of intensive care unit and hospital stays were 6.4 ± 4.3 and 18 ± 12.8 days, respectively. During follow up, late mortality was seen in 28 patients (29.4%). Possible risk factors for long-term mortality were type of prosthesis, EuroSCORE ≥ 15, postoperative pacemaker implantation, respiratory infection, and haemodialysis. Among 65 long-term survivors, their activity level was good in 53 (81.5%) and poor in two.

Conclusions: Our study results demonstrated that an individually tailored approach including scheduled surgery increases short- and long-term outcomes of AVR in patients aged ≥ 70 years. In addition, shorter cardiopulmonary bypass time may be more beneficial in this high-risk patient population.

Keywords: aortic valve replacement, elderly, surgery, mortality

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The life expectancy of European and American populations has been steadily increasing, now exceeding 80 years of age. Over the past decade in Turkey, a modest increase has been achieved with people now reaching 76 years.[1] In response to increased lifespan, aortic valve replacement (AVR) has become widely accepted in elderly patients.

Isolated AVR has been associated with an acceptable low surgical mortality rate, with improved long-term survival and quality of life.[2] Despite all improvements, concomitant procedures and associated co-morbidities may result in high-risk surgery, which led us to consider a transcatheter approach in these patients.

In the last decade, the number of elderly patients aged 80 years or older suffering from aortic valve disease has significantly increased. In this study, we aimed to identify possible factors that may affect surgical and long-term outcomes in the light of a literature review regarding the management of aortic valve disease in the elderly.

Methods

This retrospective study included a total of 114 patients (64 males, 50 females; mean age 76.6 ± 3.6 years; range 70–87 years) with AVR alone, or combined with coronary artery bypass grafting (CABG) or mitral valve surgery, admitted between January 1990 and December 2012. The study was conducted in accordance with the principles of Declaration of Helsinki. The study protocol was approved by the institutional review board (IRB) of Kartal Kosuyolu Training and Research Hospital (IRB no: 538.38792-514.10-9472). Informed consent, which was obtained from the patients, was confirmed by the IRB.

Bileaflet prostheses were mostly used, based on our experience with mechanical valve implantation and due to the poor socioeconomic status of the country in those years. During 2012, all accessible survivors were questioned to obtain data regarding their health status, the presence of chest pain, functional grades of dyspnoea [New York Heart Association (NYHA) class], and quality of life. In total, 98.9% of the survivors ($n = 64$) completed follow up through out-patient clinic visits or phone interviews.

Adverse events were defined according to the guidelines for reporting morbidity and mortality after cardiac valvular operations.[3] Surgical mortality was defined as any death, irrespective of cause, occurring within 30 days of surgery in or out of hospital,[4] and long-term mortality was defined as any death occurring 30 days or more after surgery.[5] Postoperative disease progression was defined as bleeding, poor cardiac status, renal failure (transient or permanent need of haemodialysis), neurological events, and prolonged duration of ventilatory support/intensive care unit (ICU).

Data on the pre-, intra- and postoperative periods were obtained from hospital charts. Of 95 hospital survivors, 47 visited the out-patient clinic on a regular basis.

Table 1. Baseline demographic characteristics and clinical data

	Number	*%*
Median age (years)	76.6 ± 3.6	(70–87)
Women/men	50/64	43.8/56.1
Hypertension	88	77.2
Diabetes	26	22.8
Chronic pulmonary disease	26	22.8
Pulmonary hypertension	8	7
Cerebrovascular disease	7	6.1
Peripheral vascular disease	1	0.9
Coronary artery disease	28	24.5
Chronic renal failure	11	9.6
Dyspnoea	75	65.8
NYHA		
Class II	14	12.3
Class III	81	71.1
Class IV	17	14.9
Angina pectoris	56	49.1
Previous MI	33	28.9
EuroSCORE < 15	91	79.8
> 15	23	20.2

NYHA: New York Heart Association; MI: myocardial infarction.

Pre-operative patient characteristics

The study consisted of 114 patients, including 22 (19.3%) aged ≥ 80 years. The mean age was 76.6 ± 3.6 years (range 70–87). Baseline demographic characteristics and clinical data are presented in Table 1.

A total of 110 patients (87.7%) had at least one or more extra-cardiac co-morbidity, such as pulmonary disease (n = 26), cerebrovascular accident (n = 7), peripheral artery disease (n = 1), or renal failure (n = 11). Coronary angiography revealed significant lesions in 28 patients (24.5%), including five with left main coronary artery disease (LMCA). Twenty-three patients (20.2%) had logistic EuroSCORE ≥ 15. Ninety-eight patients (86%) had NYHA (LMCA) class III–IV symptoms, whereas 16 patients (14%) had clinical manifestations of congestive heart failure.

Seventeen patients (14.9%) had chronic atrial fibrillation, including two with a pacemaker. The common pathology of the valve was aortic stenosis in 97 patients (85.1%), while 22 (19.3%) had concomitant aortic regurgitation. Only 17 patients had uncomplicated pure regurgitation. Transthoracic echocardiography showed that 10.5% of patients (n = 12) had poor left ventricular function, defined as LVEF < 40% (Table 2).

Table 2. Pre-operative measurements

	Number	*%*
Pre-operative AF	17	14.9
Pacemaker	2	1.8
Echocardiography		
Aortic stenosis (AS)	97	85.1
Aortic regurgitation (AR)	22	19.3
LVEF (mean)	56.9 ± 9.3	(35–78)
LVEF < 40%	12	10.5
Aortic area (cm^2)	0.8 ± 0.3	(0.4–1.35)
Max gradient (mmHg)	81.2 ± 25	(0–160)
Mean gradient (mmHg)	50.3 ± 16.4	(0–110)

AF: atrial fibrillation; LVEF: left ventricular ejection fraction.

Surgical data

A median sternotomy was performed in all patients. Cardiopulmonary bypass (CPB) equipment was uniform: systemic moderate hypothermia was employed along with antegrade ± retrograde isothermic blood perfusion in case of aortic valve regurgitation. Three patients (2.6%) had a history of previous CABG surgery.

A mechanical valve was implanted in all but 22 patients (19.2%) received bioprosthetic valves. The proportion of bioprothetic valve replacement was higher in patients aged ≥ 80 years (27.2 vs 17.3%). We mostly used bileaflet prostheses based on our experience with mechanical valve implantation and due to the poor socio-economic status of the country in those years.

Isolated aortic valve replacement was performed in 61 patients (53.5%), whereas 29 underwent concomitant CABG surgery, 12 received mitral valve surgery, and 13 patients received interpositional graft replacement of the ascending aorta, including a flanged Bentall de Bono procedure due to type I dissection in one patient. The mean CPB time was 139.9 ± 73.7 min, while the mean aortic cross-clamp time was 96 ± 41.5 min (Table 3).

Sixty patients (52.6%) required inotropic support for haemodynamic recovery, either in the operating room or during the postoperative period. Twelve received intra-aortic balloon pump (IABP) support. The chi-square test showed a significant correlation between the logistic EuroSCORE and inotropic support. In addition, 19 patients (82.6%) with EuroSCORE ≥ 15 needed pharmacological support (p = 0.001). Patients with LMCA stenosis (p = 0.008), NYHA ≥ 3 (p = 0.033) and EuroSCORE ≥ 15 (p = 0.002) were found to be correlated for the use of IABP.

International normalised ratio (INR) levels were measured daily and postoperative anticoagulant therapy was administered with oral sodium warfarin in all patients. Three-month therapy following bioprosthetic valve replacement was prescribed.

Statistical analysis

Statistical analysis was performed using the SPSS software v12.0 (SPSS Inc, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation or percentages. The Student's t-test and Mann–Whitney U-test were used to compare differences among the variables.

Table 3. Intra-operative data

	Number	*%*
Re-operation	6	5.2
Isolated AVR	61	53.5
AVR+ concomitant surgery		
CABG	29	25.4
Mitral valve surgery	12	10.5
CABG + MVR	1	0.8
Tubular graft interposition	13	11.4
Valve size (mm)	2.89	
Aortic cross clamping time (min)	96 ± 41.5	(26–240)
Cardiopulmonary bypass time (min)	139.9 ± 73.7	(46–480)
Postoperative inotropic support	60	52.6
IABP support	12	10.5

AVR: aortic valve replacement; CABG: coronary artery bypass grafting; MVR: mitral valve replacement; IABP: intra-aortic balloon pump.

One-way analysis of covariance (ANOVA) and the Tukey *post hoc* analysis were used to compare three or more normally distributed samples. In the case of abnormally distributed data, the Kruskal–Wallis test was used for more than three samples, whereas the Mann–Whitney *U*-test was used to compare two samples based on the adjusted Bonferroni correction. The cross tabulation table was used to compare categorical variables (chi-square, Fisher, Mantel–Haenszel test).

All variables were initially tested individually by univariate analysis. Then, variables with a *p*-value of ≤ 0.25 in univarate analysis were applied into the logistic regression model to identify independent predictors for mortality. Late survival rates were calculated using the Kaplan–Meier method and statistical significance was calculated with the log-rank test. A *p*-value of < 0.05 was considered statistically significant.

Results

The mean follow up was 48.7 ± 50.8 months (range 0–240). Early postoperative complications are listed in Table 4. Arrhythmias occurred in 26 patients (22.8%), of whom 13 had atrial fibrillation. All received medical therapy. The other 13 (11.4%) needed permanent pacemaker implantation. Despite optimal selection of the prosthesis to minimise the incidence of pacemaker implantation, we found no correlation among peri-operative risk factors, including prosthesis type ($p = 0.457$). However, pre-operative values of NYHA ($p < 0.001$) and logistic EuroSCORE ($p = 0.023$) were found to be significantly correlated with peri-operative risk factors.

Renal failure was present in 11 patients (9.6%), of whom seven patients needed transient haemodialysis after surgery. Four (3.5%) required long-term haemodialysis. Among 30 patients (26.3%) requiring prolonged mechanical ventilation (> 24 hours), nine (7.9%) had respiratory infection. There was a significant correlation between LMCA stenosis and infection ($p = 0.049$).

Three patients (2.6%) developed cerebrovascular accident and two recovered fully before hospital discharge. Six patients needed re-operation, of whom three were operated on due to excessive bleeding. The rest were operated on for cardiac tamponade. The mean length of ICU and hospital stay was 6.4 ± 4.3 and 18 ± 12.8 days, respectively.

In-hospital mortality was seen in 19 patients (16.7%). The mortality rate was 8.7% in 10 patients who underwent isolated AVR. The mean time to death after surgery was 17 ± 15.61 days (range 0–48 days). The major causes of in-hospital mortality were low-cardiac output syndrome in eight patients (42.1%), respiratory insufficiency or infection in six (31.5%), multi-organ failure in four (21%), and stroke in one patient (5.2%). Univariate analysis revealed the following variables to be associated with operative mortality: LMCA stenosis ($p = 0.032$), NYHA ≥ III ($p = 0.002$) and EuroSCORE ≥ 15 ($p < 0.001$).

Table 4. Postoperative complications

Variable	*Number*	*%*
Arrhythmia	26	22.8
Pacemaker implantation	13	11.4
Prolonged mechanical ventilation	30	26.3
Bleeding total (ml)	641 ± 480.56	
Re-operation		
Bleeding	3	2.6
Tamponade	3	2.6
Cerebrovascular accident	3	2.6
Renal failure	11	7.9
Haemodialysis (permanent)	4	3.5
Pulmonary failure	9	7.9

During the follow-up period, 28 late deaths (29.4%) occurred. A total of 98.9% completed the follow-up period. Based on the univariate analysis, possible risk factors for long-term mortality were type of prosthesis ($p = 0.037$), EuroSCORE ≥ 15 ($p = 0.013$), postoperative pacemaker implantation ($p = 0.008$), respiratory infection ($p = 0.004$), and haemodialysis ($p = 0.004$). Mortality rate was higher in the mechanical valve group. Multivariate analysis identified the following variables as independent predictors of mortality: cross-clamp time ($p = 0.043$) and CPB time ($p = 0.033$).

Furthermore, although cerebrovascular accidents, either from intracranial haemorrhage or ischaemic stroke, were the leading cause of death ($n = 8$). Respiratory failure ($n = 7$) and cardiovascular disease ($n = 6$) accounted for 46.4% of the late mortalities. Three patients died from renal insufficiency, while one had a neoplasm, one had mesenteric ischaemia, and two patients suffered from sudden death.

One, three, five, 10 and 15-year survival rates were 76.2 ± 4.12, 69.03 ± 4.44, 61.40 ± 5.13, 43.48 ± 7.42 and 24.15 ± 9.65%, respectively (Fig. 1). Patients with combined surgery showed lower survival rates (log-rank, $p = 0.0498$) (Fig. 2).

During follow up, late complications were intracranial haemorrhage in one patient, stroke in one patient and re-operation for vegetations and paravalvular leakage in two patients (at 10 years and one year after the initial surgery, respectively).

The patients were questioned on symptom relief and an active lifestyle. Among 65 long-term survivors, activity level was good in 53 (81.5%) and poor in two (3.1%). The patients reported improved quality of life compared to their pre-operative status. We were unable to reach 10 patients to determine their activity levels.

Discussion

Since 1970, men and women worldwide have gained slightly more than 10 years of life expectancy overall, but they spend more years living with injury and illness. Non-communicable diseases, such as cancer and heart disease, have become the dominant causes of death and disability worldwide.[6]

With the introduction of improved surgical techniques and prolonged life expectancy, an increasing number of elderly people are considered candidates for valve surgery. According to the Euro Heart Survey, intervention was rejected in up to 33% of patients, despite their severe symptomatic aortic stenosis (AS) status.[7] However, the natural prognosis of severe AS is associated with a life expectancy of less than five years.[8,9] In our study, we found that mortality rates in elderly patients (≥ 70 years) who underwent timely aortic valve operations were very low. This encourages us to refer especially the elderly with aortic stenosis for surgery.

Several studies have showed that valve replacement can be performed with an acceptable mortality rate and high long-term survival rate.[10-12] Kohl *et al.*[13] reported their operative mortality

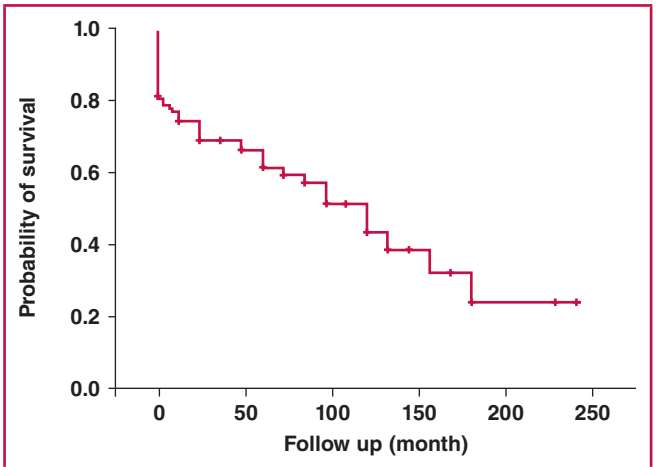

Fig. 1. Probability of survival.

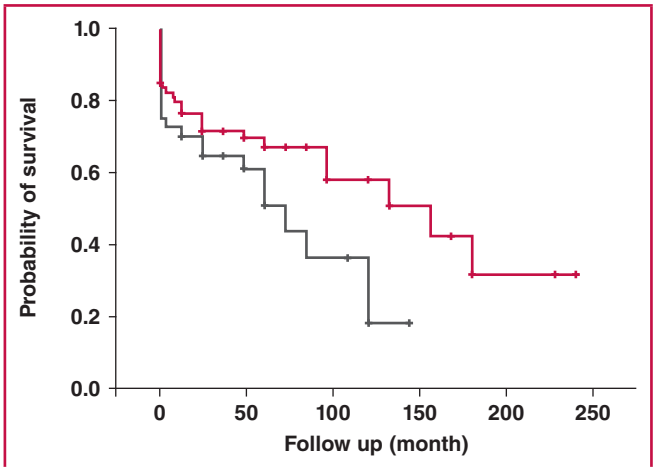

Fig. 2. Survival rates in the combined surgery group.

rate to be 13%, which was increased to 24% with combined surgery.[13] In our study, in-hospital mortality was 8.7% in patients with isolated AVR and 16.7% in patients with combined surgery. In addition, early reports in the elderly have shown mortality rates of 2–10% for isolated AVR.[14,15]

Concomitant CABG was also identified as an independent predictor in a clinical series.[16] However, in a study including 450 patients aged ≥ 80 years, Unic *et al.*[17] showed that concomitant CABG did not affect the late survival rate.

In our study, we did not find any correlation between combined surgery and mortality rate. Even though LMCA stenosis, NYHA ≥ III and EuroSCORE ≥ 15 were associated with early mortality in the univariate analysis, multivariate logistic regression analysis revealed that the only risk factor associated with surgical mortality was CBP time, as anticipated. In other words, simple operations with shorter CPB times may be more beneficial than better complex operations with longer CPB times in high-risk patients.

In addition, our study findings confirmed that patients undergoing combined surgery with concomitant CABG showed lower long-term survival rates compared to surgical mortality rates, from 16.7% post operatively to 13.3% long-term survival. This is noticeably lower than the 24% early mortality that was reported by Kolh *et al.*[18] Kurlansky *et al.*[16] also identified concomitant CABG as a predictor of mortality; however, they showed the improvement in quality of life in the long term.

In our study, mitral valve surgery was associated with an increased mortality rate (30.1%). This was consistent with a number of previous studies.[15,19] It has been reported that AVR can be performed in elderly patients with an acceptable mortality rate, high long-term survival rate and functional improvement.[14,20] One-, three- and five-year survival rates were 76.2 ± 4.12, 69.03 ± 4.44 and 61.40 ± 5.13%, respectively. However, these rates need to be confirmed.[13,14]

The low survival rates in our study can be attributed to multiple factors, including that 87.7% of patients had extracardiac co-morbidities; 10.5% had poor ejection fraction, and 86% were in NYHA class ≥ III. Postoperative pacemaker, respiratory infection and haemodialysis were predictors for late mortality, while aortic cross-clamp time and CPB time were found with multivariate analysis to be independent predictors of mortality. These results suggest that combined surgery entails prolonged ischaemic time, leading us to tailor an appropriate surgical strategy for each patient.

The use of bioprosthetic valves, which allow for implantation of larger prostheses, was lower than in previous studies. The early experiences of Peterseim *et al.*[21] reported that bioprostheses should be considered in patients with a number of co-morbidities or aged ≥ 65 years. In a retrospective study, however, Silberman *et al.*[22] reported that the selection of valve replacement device should be based on life expectancy, patient preference, lifestyle and surgery-related complications.

The limitations of the present study include missing information due to limited data collection, as it was a retrospective study, and missed regular out-patient visits. Although 98.9% of patients completed the follow-up period, less attention was paid to the quality of life. Among long-term survivers, only two patients had poor activity levels. However, the Short form 36 health survey should be completed for further investigation of long-term quality of life.

Conclusion

It is obvious that we need more surgical experience on elderly patients. Our study results demonstrate that an individually tailored approach including scheduled surgery increased short- and long-term outcomes of AVR in patients aged ≥ 70 years. In addition, shorter cardiopulmonary bypass time may be more beneficial in this high-risk patient population.

Although several issues should be considered for elderly patients undergoing cardiac surgery, including socio-economic factors, the possible benefits of surgery should not be ignored in patients with aortic valve disease who are eligible for surgery. In addition, in the presence of combined cardiac procedures, a hybrid approach or transcatheter aortic valve implantation with isolated conventional AVR may be an alternative in high-risk patients.

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Glucose 'control switch' in the brain key to both types of diabetes

Researchers at Yale School of Medicine have pinpointed a mechanism in part of the brain that is key to sensing glucose levels in the blood, linking it to both type 1 and type 2 diabetes. The findings were published in the July 28 issue of *Proceedings of the National Academies of Sciences*.

'We've discovered that the prolyl endopeptidase enzyme' located in a part of the hypothalamus known as the ventromedial nucleus, sets a series of steps in motion that control glucose levels in the blood', said lead author Sabrina Diano, professor in the Departments of Obstetrics, Gynecology and Reproductive Sciences, Comparative Medicine, and Neurobiology at Yale School of Medicine. 'Our findings could eventually lead to new treatments for diabetes.'

The ventromedial nucleus contains cells that are glucose sensors. To understand the role of prolyl endopeptidase in this part of the brain, the team used mice that were genetically engineered with low levels of this enzyme. They found that in the absence of this enzyme, mice had high levels of glucose in the blood and became diabetic.

Diano and her team discovered that this enzyme is important because it makes the neurons in this part of the brain sensitive to glucose. The neurons sense the increase in glucose levels and then tell the pancreas to release insulin, thus preventing diabetes.

'Because of the low levels of endopeptidase, the neurons were no longer sensitive to increased glucose levels and could not control the release of insulin from the pancreas, and the mice developed diabetes', said Diano, who is also a member of the Yale program on integrative cell signalling and the neurobiology of metabolism.

Diano said the next step in this research is to identify the targets of this enzyme by understanding how the enzyme makes the neurons sense changes in glucose levels. 'If we succeed in doing this, we could be able to regulate the secretion of insulin, and be able to prevent and treat type 2 diabetes', she said.

Source

http://medicalxpress.com/news/2014-07-glucose-brain-key-diabetes.html

Letter to the Editor

Efficacy and safety of sirolimus-eluting stents versus bare-metal stents in coronary artery disease patients with diabetes

Dear Sir

I read with great interest the recent article titled 'Efficacy and safety of sirolimus-eluting stents versus bare-metal stents in coronary artery disease patients with diabetes: a meta-analysis' by Qiao *et al*., published online in the *Cardiovascular Journal of Africa*.[1] I believe this is a well-conducted meta-analysis that compared the major cardiac events, target-lesion revascularisation, myocardial infarction and mortality rate in coronary arterial disease (CAD) patients with diabetes who were treated with sirolimus-eluting stents (SES) or bare-metal stent (BMS). However, there are some issues I would like to point out.

The electronic databases (PubMed, MEDLINE, EMBASE, Springer, Elsevier Science Direct, Cochrane Library and Google scholar) were systematically searched by the authors. However, they did not describe the search strategy for databases in detail, which plays an important role in systematic reviews. The manual searches were not clearly described. The lack of a manual search protocol may be considered a weakness of the meta-analysis.

The publication language in this meta-analysis was limited to English but the authors did not mention it in the discussion. Therefore, there may have been a language bias in their meta-analysis. I suggest that there be no language limitation for the included studies to reduce the bias.

The inclusion and exclusion criteria were not adequately described in this meta-analysis. I suggest that explicit inclusion and exclusion criteria be introduced in detail.

The publication bias in this meta-analysis was evaluated with Egger's test and funnel plots. However, the number of studies was less than 10, and as far as I know, a funnel plot should be inspected visually to assess for publication bias in meta-analyses with at least 10 studies. Therefore, it was inappropriate.

Under the statistical analysis heading, the authors wrote 'Pooled ORs were obtained using the Mantel-Haenszel method in a fixed-effect model, and the DerSimonian-Laid method in a random-effects model'. However, it is not appropriate to use the Mantel-Haenszel method in a random-effects model to pool the data for all forest plots, regardless of heterogeneity.

It is very important in meta-analyses to evaluate methodological quality of included studies. However, the authors did not provide any methodological quality assessment or detailed scores for each trial in this article.

In conclusion, I agree with the results of this meta-analysis. SES are safer and more effective than BMS in CAD patients with diabetes, as far as major cardiac events are concerned. To reach a definitive conclusion, however, more high-quality studies with larger sample sizes are needed.

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Conference Report

The way forward for clinical research in Cameroon: First scientific and research day in Douala, 2014

Abstract

There is a huge need for health research to support contextually relevant health service and policy solutions to better the health of populations in sub-Saharan Africa. This need contrasts with the very timid engagement of healthcare practitioners in research in the region.

It is against this background that the Douala General Hospital (a tertiary-care hospital in Cameroon), under the stewardship of its chief executive officer, organised the first annual scientific and research day in October 2014. This maiden event saw the participation of local research leaders and the eminent director of the South African Hatter Institute for Cardiovascular Research in Africa, who co-chaired the event. The aim was to educate students, clinicians and junior researchers on the importance of clinical research and evidence-based medicine around the leading theme of the event: action for clinical research and good medical practice.

Several abstracts were presented, covering various aspects of medicine, including cardiology, rheumatology, paediatrics, pulmonology, HIV medicine, and obstetrics and gynaecology, together with key lectures on cardiac disease and pregnancy, and plenary sessions on research methodology, scientific writing and publishing. It is hoped that this event will enhance clinical research and the dissemination of research findings to improve evidence-based clinical practice in the country.

Background

Clinical research in sub-Saharan Africa (SSA) is very daunting due to the combined effects of many factors, including the timidity for, or lack of interest of clinicians in research, the absence of adequate infrastructure for the conduct of clinical and experimental research, a structured health system that is not conducive to research, as well as funding constraints.[1] In order to foster good clinical practice and evidence-based medicine, executives of the Douala General Hospital (DGH), which is a referral hospital for Cameroon and central Africa, initiated the annual research and scientific day and organised the maiden event on 2 October 2014. The technical organisation was done by experts from the Clinical Research Education, Networking and Consultancy (CRENC), and the Cameroon Cardiac Society, and they were advised by the Pan-African Society of Cardiology.

The main theme of this conference was 'action for clinical research and good medical practice'. This event brought together over 200 participants, including general practitioners, surgeons, obstetricians, cardiologists, endocrinologists, specialist physicians in training, undergraduate medical students and medical researchers. It was co-chaired by Prof Karen Sliwa-Hahnle, director of the Hatter Institute for Cardiovascular Research in Africa (HICRA), University of Cape Town, South Africa, who is also director of the Soweto Cardiovascular Research Unit, University of Witwatersrand, South Africa. As a clinical cardiologist and a renowned clincal researcher, her participation was in line with her vision, plans and commitment for health research in Africa, as reflected in this quote from her on that day: 'We know the major problems of cardiovascular disease on the continent. What we need are the solutions, not further documentation of the problems of hypertension, obesity and related lifestyle factors'.

There is no doubt that Prof Sliwa-Hahnle's presence in Cameroon on this occasion gave an additional flavour to the event.[2] The conference was enlightening, with a session for abstract presentations (orally and by poster), followed by plenary sessions on cardiac disease and pregnancy, research methodology, ethics and research in Cameroon, and the art and impact of scientific writing and publishing. Finally, awards were given for the best abstracts.

Opening ceremony and abstracts session

The opening ceremony was chaired by Prof Henry Luma, medical director of DGH, who welcomed all participants and called upon them to contribute to improvement in research in Cameroon. Then followed the abstract presentations on various topics, including hypertension, prediction algorithms, antibiotic use, heart failure, outcomes of newborns, adherence to antiretroviral medication, osteoarthritis and the epidemiology of thunderclap headaches.

Dr Tianyi Tianyi (Cameroon) presented a community-based study on the association of hypertension with cognitive impairment among elders in the rural area of Batibo in the north-west region of Cameroon. A third of older people in the area were cognitively impaired, with those with hypertension being significantly more affected and more likely to lose their personal independence.

Dr Pefura-Yone, a pulmonologist and lecturer at the Faculty of Medicine in Yaounde, elaborated on the need for rules for clinical prediction to improve the diagnosis of asthma, in the context of high variability of existing clinical diagnostic criteria for asthma across regions. Using a community-based sample of 1 681 participants (13.1% with asthma), he developed a simple score based on the principal symptoms, with acceptable performance in predicting the presence of asthma.

Dr Mbam Leonard, a physician in Buea (south-west region of Cameroon), discussed the irrational use and prescription of antibiotics as well as polypharmacy in Buea. In his study,

Official photo.

ceftriaxone and metronidazole appeared to be the most abused drugs in this region.

In his presentation, Dr Mapoh Sylvester revealed the increasing admission rate for heart failure at the DGH, however, with a contrasting decline in mortality rate from this disease in recent years. This is most likely explained by the recent establishment of an intensive cardiac and vascular care unit in the hospital.

Dr Tchente Charlotte, a consultant obstetrician and gynaecologist at DGH reported that respiratory distress was more common among newborns born via elective caesarian delivery prior to 39 weeks' gestation than in those born via vaginal delivery. This difference lessened with increasing gestational age.

Dr Essomba Noel and colleagues reported that being widowed, being an alcohol drinker, or having opportunistic infections were the main correlates, in regression analyses, of poor adherence to antiretroviral therapy among patients in Douala.

Dr Ako Forbang, in a study to characterise the clinical and radiological patterns and treatment options of patients with hip osteoarthritis in DGH, reviewed 9 615 cases. The prevalence of symptomatic hip osteoarthritis was 2.7%, with a preponderance of females. Patients mostly presented with pain, and the frequent radiological grade was Kellgren-Lawrence grade 4. Of those with indications for hip arthroplasty, less than 50% underwent replacement therapy, with the main constraints being financial.

The neurologist Dr Mapoure, in an effort to describe the epidemiology, aetiology and prognosis of thunderclap headaches in Douala, realised that most cases occurred spontaneously and during sexual intercourse, with the main aetiology being subarachnoid haemorrhage. Mortality rate was high, mainly from subarachnoid haemorrhage, and seizures were the main predictive factor of death.

Several posters were presented on a wide variety of topics, including excessive daytime sleepiness and hypertension by Dr Nganda Malea, post-exposure prophylaxis for HIV by Dr Aminde Leopold, survival of stroke patients by Dr Mapoure, hypertension in rural Cameroon by Dr Arrey Walters, vitamin changes in haemodialysis patients by Cedric Gueguim, and the influence of tradipractitioners' services on patients' adherence to ARVs by Dr Songo Jacques.

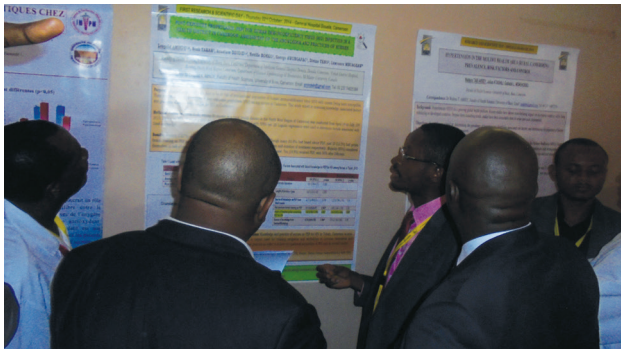
Plenary session: cardiac disease and pregnancy

This session was co-chaired by the chief executive officer of the Douala General Hospital, Prof Eugene Belley Priso, the director of the HICRA, Prof Karen Sliwa-Hahnle, and the dean of the Faculty of Medical and Pharmaceutical Sciences, University of Douala, Prof Albert Mouelle Sone. Prof Sliwa-Hahnle gave a very well-attended lecture on recent advances in cardiac disease in pregnancy. She elaborated on her novel discoveries on the pathogenesis of peripartum cardiomyopathy (PPCMP), with a sub-type of prolactin being the origin of the myocardial changes consistent with PPCMP. She went on to demonstrate research evidence and promising successes in the treatment of the condition using bromocriptine in rats and mice. She then discussed possible differential diagnoses of PPCMP, and provided an algorithm for the diagnosis of PPCMP.

Prof Sliwa-Hahnle's lecture also focused on the updated European Society guidelines for the management of cardiac diseases in pregnancy. She concluded by calling on all participants

Audience during the plenary session.

Poster session 1.



Poster session 2.

Group picture.

to be aware of the prevalence of PPCMP, and the multidisciplinary approach to the condition, involving at least a cardiologist, obstetrican–gynaecologists and anaesthesiologists. An intensive discussion followed on the appropriate referral algorithm and risk stratification for women in low-income countries, such as Cameroon.

Research methodology

This session was co-chaired by Profs Sliwa-Hahnle and Henry Luma, and Dr Mbatchou Hugo. Prof Luma gave a lecture on the current opportunities and challenges for research at DGH. The main difficulties were linked to lack of team spirit, and the absence of adequate infrastructure and limited funding for research. Collaboration with other institutions and universities at national and international levels were the proposed solutions for capitalising on opportunities.

In an educational lecture on epidemiological studies with emphasis on study design, delivered by Dr Julius Atashili (lecturer and clinical epidemiologist at the Faculty of Health Sciences, University of Buea), he enlightened participants on the variation in classification of epidemiological studies and outlined the pros and cons of various study types and designs.

Dr Temfack Elvis presented on the process of formulating and implementing a research question as well as study hypothesis. This was followed by a lecture on ethical issues in research by Dr Doualla Marie Solange and the importance of ethical and administrative approval prior to conducting research. Dr Armand S Nkwescheu from the Unit of Scientific Networks and Ethics Promotion at the Cameroon Ministry of Public Health highlighted the fact that the establishment of a formal ethics committee is urgently needed to be formalised at all health institutions, so as to enable good research practices.

The session ended with a presentation by Dr Anastase Dzudie (a member of the CRENC, assistant PASCAR general secretary of the central region and regional editor for the *Cardiovascular Journal of Africa*) on the art, essence and significance of scientific writing and publishing. He also elaborated on the challenges faced by authors and journal editors in the publication process.

Young researcher awards

The following were laureates for the top abstracts: for the oral communications, Dr Tianyi Tianyi Frank won the price for the best presentation, followed by Dr Mapoh Sylvester and third was Dr Tchente Nguefack. For the poster presentations, Dr Nganda Malea and Dr Aminde Leopold won prices for the best presentations.

Conclusion

This first scientific and research day achieved its objective of bringing together students, clinicians and junior researchers in Cameroon. It is hoped that this will serve as a catalyst for greater collaboration as well as re-ignite the quest for research and dissemination of research findings in Cameroon and beyond. However, there are some important aspects that need to be urgently formalised in this setting, including the establishment of a formal ethics committee, implementation of a recognised good clinical practice (GCP) course, as well as a dedicated programme for trainees to learn about research methodology. It is hoped that the partnerships forged between DGH and other institutions will provide opportunities for such training and collaborative research as well as student exchange.

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Case Report

Surgical treatment of post-infarct left ventricular pseudo-aneurysm with on-pump beating heart technique

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Abstract

Left ventricular pseudo-aneurysms develop when cardiac rupture is contained by pericardial adhesions or scar tissue due to myocardial infarction, surgery, trauma or infection. Left ventricular pseudo-aneurysms are uncommon, difficult to diagnose and prone to cardiac rupture. Urgent surgical repair is recommended. Here we report on a case of a large left ventricular pseudo-aneurysm on the anterolateral wall due to a previous anterior myocardial infarction, and its successful repair using the on-pump beating-heart technique.

Keywords: left ventricular pseudo-aneurysm, repair, on-pump beating heart

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Left ventricular (LV) free wall rupture is a fatal complication of myocardial infarction (MI). Its prevalence is 4% in patients with MI.[1,2] On the other hand, when the cardiac rupture is unrecognised and contained by pericardial adhesions, organising thrombus and haematoma, a LV pseudo-aneurysm develops. Acquired LV pseudo-aneurysms may develop after transmural MI (55%), surgery (33%), trauma (7%) or infection (5%).[3]

Since it is a rare complication, the natural progression of LV pseudo-aneurysm is not well known. When a LV pseudo-aneurysm is detected, urgent surgical repair is recommended because of the possibility of complete rupture and the risk of fatal cardiac tamponade.[4] Here we report on a case with a large LV pseudo-aneurysm on the anterolateral wall due to a previous anterior MI and its successful repair using the on-pump beating-heart technique (ONCAB/BH).

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Case report

A 62-year-old woman with history of prior anterior MI presented to our clinic with symptoms of shortness of breath at rest and palpitations. Five months previously, the patient was treated with a stent implantation to the left anterior descending artery (LAD). A chest X-ray showed an enlarged heart with an aberrant contour in the lateral projection (Fig 1A).

An electrocardiogram examination revealed persistent ST-segment elevation in leads V2–V4. Echocardiography showed a 6 × 6 × 4-cm limited mushroom-shaped anechoic area at the anterolateral wall of the LV, mild mitral valve regurgitation and severe LV dysfunction with an ejection fraction of 32% (Fig. 1B).

Coronary angiography revealed 90% stenosis of the first diagonal branch of the LAD and 80% stenosis of the first obtuse marginal branch of the circumflex artery. There was no significant stenosis in the LAD.

Urgent surgery was conducted through a median sternotomy. Standard cannulation of the aorta and right atrium was done and the operation was carried out using normothermic cardiopulmonary bypass (CPB). The pseudo-aneurysm extended to the anterolateral side of the LV wall and was contained by pericardial adhesion.

The LV was gently dissected free from the pericardium. A piece of the pericardium was left at the site of the pseudo-aneurysmal sac. The sac of the pseudo-aneurysm was incised. There were no clots in the pseudo-aneurysm. The defect in the myocardium forming the neck of the pseudo-aneurysm was detected.

The neck of the pseudo-aneurysm was fused with thick, firm endocardium using separate full-thickness U sutures (Fig. 2A), and closed by creating a longitudinal plication line, which was buttressed with Teflon felt strips (Fig. 2B). The necrotic part of the LV wall was removed (Fig. 2C) and the plication was strengthened with sutures.

Following surgical repair of the LV pseudo-aneurysm, sequential coronary artery bypass venous grafting was performed to the first diagonal branch of the LAD and the first obtuse marginal branch of the circumflex artery (Fig 2D). The operation was performed with ther normothermic ONCAB/BH technique.

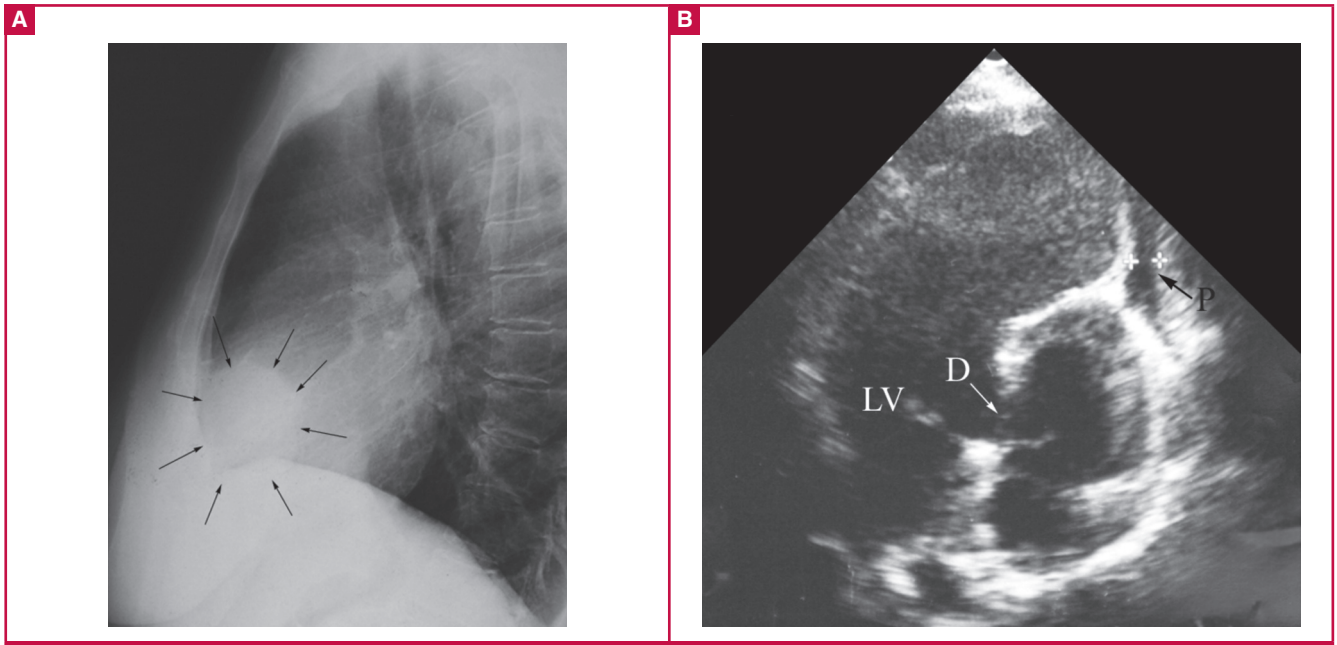

Fig. 1. (A) Pre-operative chest X-ray (lateral projection) visualising the aberrant contour of the LV pseudo-aneurysm. (B) Pre-operative transthoracic echocardiography demonstrating the anterolateral pseudo-aneurysm (LV: left ventricle, D: defect, P: pericard).

The patient was weaned uneventfully from CPB without inotropic support. The postoperative course was uneventful and the patient was discharged on the sixth postoperative day.

At the one-year follow up, the patient reported an active life. Echocardiography revealed an ejection fraction of 53% and satisfactory LV remodelling.

Discussion

LV pseudo-aneurysm develops when a free-wall rupture is contained by overlying adherent pericardium.[4] A small, narrow-necked channel connects the LV with the sac. A LV pseudo-aneurysm does not contain an endocardial or myocardial layer of the LV wall.[5] By contrast, a true LV aneurysm is a result of the thinning of the LV wall due to scar formation after MI.

Pseudo-aneurysms may lead to fatal rupture at any time after MI, or to arrhythmia, cardiac dysfunction or emboli.[6] Eren *et al.* reported the rate of incidence of pseudo-aneurysms between 31 and 45%.[1]

The most common cause of pseudo-aneurysms is an MI due to the occlusion of the right coronary or LAD artery.[7] One-third of pseudo-aneurysms are due to a complication of cardiac surgical procedures, mostly mitral valve replacement.[5] Other aetiological factors are infection and trauma.[3]

LV pseudo-aneurysms are usually asymptomatic, and are recognised on investigation for other conditions, mostly congestive heart failure (36%), chest pain (30%) or dyspnoea (25%).[5] Other presentations are arrhythmia and embolisation.[1] Our patient had a history of anterior MI, and hence the complaint of dyspnoea at rest and palpitations as symptoms of congestive heart failure.

Computed tomography, echocardiography and magnetic resonance imaging are helpful in the pre-operative diagnosis but coronary angiography and contrast ventriculography are necessary to evaluate the coronary arteries and precise localisation of the pseudo-aneurysm.

The timing of surgery depends on time since the MI. Urgent surgical repair is recommended if the pseudo-aneurysm is detected early after MI because of the risk of rupture.[8] The rate of incidence of cardiac rupture in untreated pseudo-aneurysms ranges from 30 to 45%.[5] However, with chronic pseudo-aneurysms, the symptoms are more important than the risk of rupture in determining the necessity of operation.[9]

Yeo *et al.* treated 10 patients with pseudo-aneurysm conservatively and in none of the cases was cardiac rupture documented after a median follow up of 2.3 years.[10] Moreno and colleagues treated nine patients with LV pseudo-aneurysm conservatively and reported a cumulative survival of 88.9 and 74.1% at one year and four years, respectively.[4] The rate of incidence of mortality after surgical repair of LV pseudo-aneurysms ranges from 13 to 29%.[4]

The rate of intra-operative and post-operative complications due to the use of CPB and cardioplegic arrest is low in low-risk patients, but the scenario is different when the technique is applied to high-risk groups, or patients requiring emergency surgery.[11] Complications related to conventional CPB are due to the release of inflammatory mediators, the administration of cardioplegia, aortic cross-clamping and hypothermia.[12]

On the other hand, the off-pump technique can cause episodes of transitory haemodynamic deterioration that could result in inadequate coronary artery blood flow, followed by severe complications or death.[13] Perrault *et al.* proved that the ONCAB/BH technique, which represents the idea of using CPB without cross-clamping and cardioplegic arrest, with the heart beating, can be effectively used in high-risk patients who cannot tolerate cardioplegic arrest, and is associated with less myocardial oedema and ischaemia.[14] The benefits of this technique are the absence of cardioplegic arrest (global myocardial ischaemia

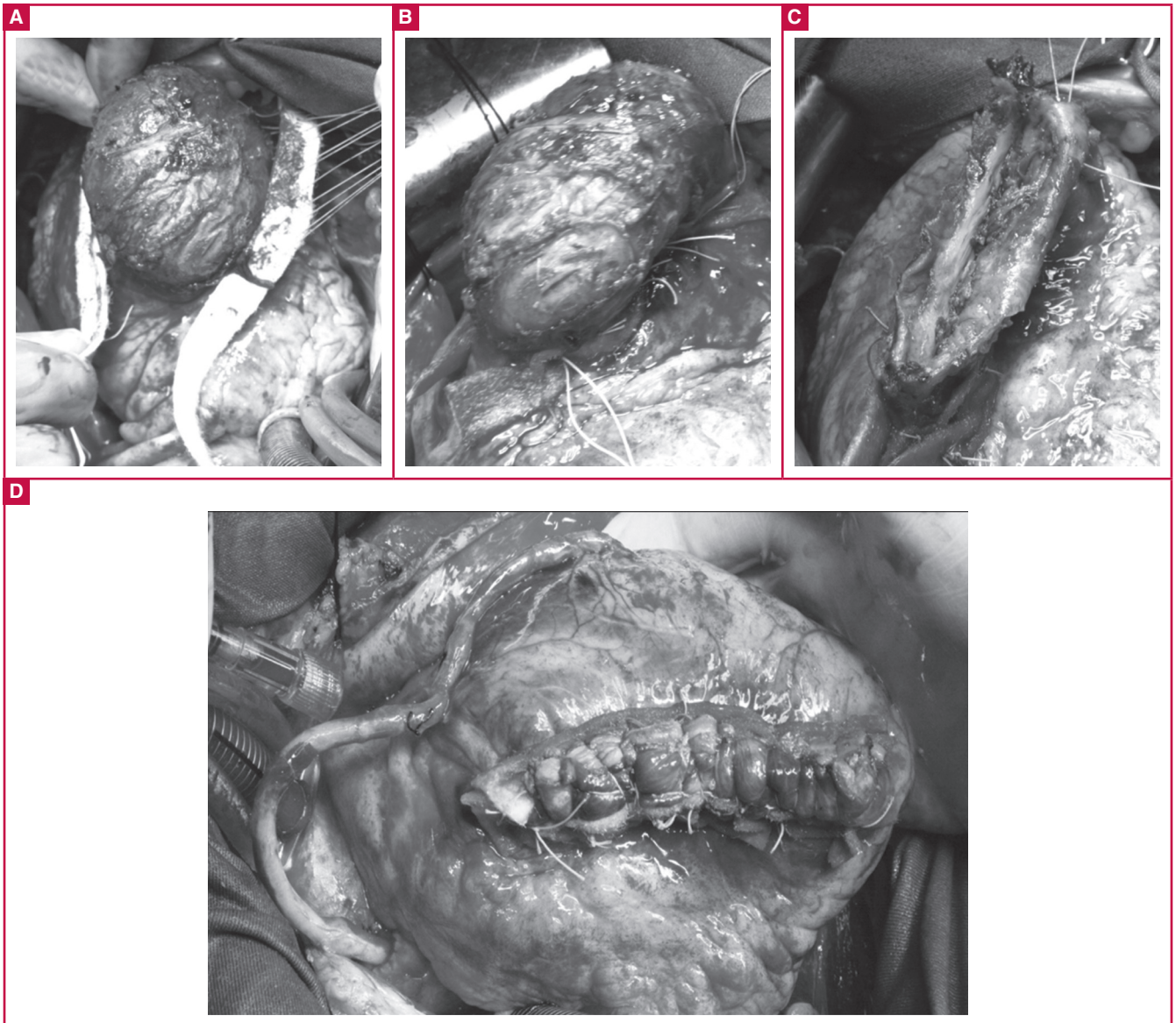

Fig. 2. (A) Full-thickness U sutures (0 Ethibond) passed from strips of Teflon and stable endocardium. (B) Longitudinal plication line, which was buttressed by Teflon felt strips. (C) The necrotic part of the left ventricular wall was removed. (D) The plication was strengthened with sutures and sequential coronary artery bypass venous grafting was performed to the first diagonal branch of the left anterior descending artery and the first obtuse marginal branch of the circumflex artery.

during aortic cross-clamping time followed by reperfusion) and the reduction in haemodynamic instability caused by extensive surgical manipulation of the heart.

Patients presenting with LV pseudo-aneurysm are usually high-risk patients with low ejection fraction. Our patient's pre-operative ejection fraction was 32%. As we achieved complete revascularisation in our patient, ONCAB/BH eliminated the difficulty of grafting the circumflex and posterior descending coronary arteries. We performed longitudinal plication before resection of the necrotic muscle to prevent air embolism as well as to provide clear and bloodless surgical exposure.

Conclusion

The rare but fatal complication of MI, LV pseudo-aneurysm, can be surgically repaired using the on-pump beating heart and longitudinal plication technique so that the patient does not develop LV thrombus.

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Case Report

Traumatic aortic regurgitation combined with descending aortic pseudoaneurysm secondary to blunt chest trauma

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Abstract

Rupture of the aorta is a relatively rare complication of blunt chest trauma, and traumatic rupture of the aortic valve is even rarer. Even though both result from blunt chest trauma, the causative mechanisms of aortic valve injury differ from those of descending aortic rupture. There are no previous reports in the literature of simultaneous injuries to both the descending aorta and the aortic valve. We report a case of a 70-year-old man who presented with traumatic aortic regurgitation combined with traumatic pseudoaneurysm of the aortic isthmus following blunt chest trauma, and its successful repair with a hybrid surgical strategy.

Keywords: chest trauma, aortic regurgitation, aortic pseudoaneurysm

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Acute traumatic aortic injury is a rare complication of blunt chest trauma that can lead to aortic rupture, and traumatic aortic regurgitation is an extremely rare complication of cardiac trauma.[1-3] Both complications generally originate after severe multiple injuries to the thorax. However, it is known that the causative mechanisms of aortic valve injury differ from those of descending aortic injury.[2]

There are a few reports in the literature concerning single lesions or aortic valve injury together with ascending aortic rupture.[3] However, to the best of our knowledge, there are no previous case reports of simultaneous injuries to both the descending aorta and the aortic valve. We report a case of a 70-year-old man who presented with traumatic aortic regurgitation combined with traumatic aortic pseudoaneurysm of the aortic isthmus following blunt chest trauma.

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Case report

A 70-year-old man was admitted to our hospital after a car accident. He had a medical history of hypertension over the past three years but no past history of suspected cardiovascular disease such as valve disease or thoracic aortic aneurysm.

On physical examination, there was tenderness on the left chest wall. A chest X-ray revealed multiple rib fractures and minimal left haemothorax. Since the patient's vital signs were stable, conservative treatment for the fracture and the haemothorax was initially agreed on. However, soon after, he developed dyspnoea, dizziness and general weakness.

On further physical examination, a diastolic murmur was detected at the aortic arch, and transoesophageal echocardiography (TEE) revealed acute severe aortic regurgitation with rupture of the non-coronary cusp (Fig. 1A, B). Repeat chest X-ray also revealed aggravated pulmonary congestion. Additionally, images of computed tomography showed a small saccular pseudo-aneurysm at the isthmic portion of the aorta, which was suspected to be of traumatic origin (Fig. 1C, D).

The staged hybrid approach was chosen, which is aortic valve replacement followed by thoracic endovascular aneurysm repair to address both the aortic valve and the aortic isthmus injuries. The aortic valve replacement was performed one week after the accident.

The perforation of the non-coronary cusp was identified during surgery and the residual remnant of the cusp was found to be torn. Otherwise, the other coronary cusps were grossly normal. The aortic valve was removed and replaced with a bioprosthetic valve (Sorin Soprano no 22) (Fig. 2A, B). In addition, a stent graft (34 × 100 mm) was performed for the pseudo-aneurysm in the descending thoracic aorta 10 days after the valve operation (Fig. 2C, D).

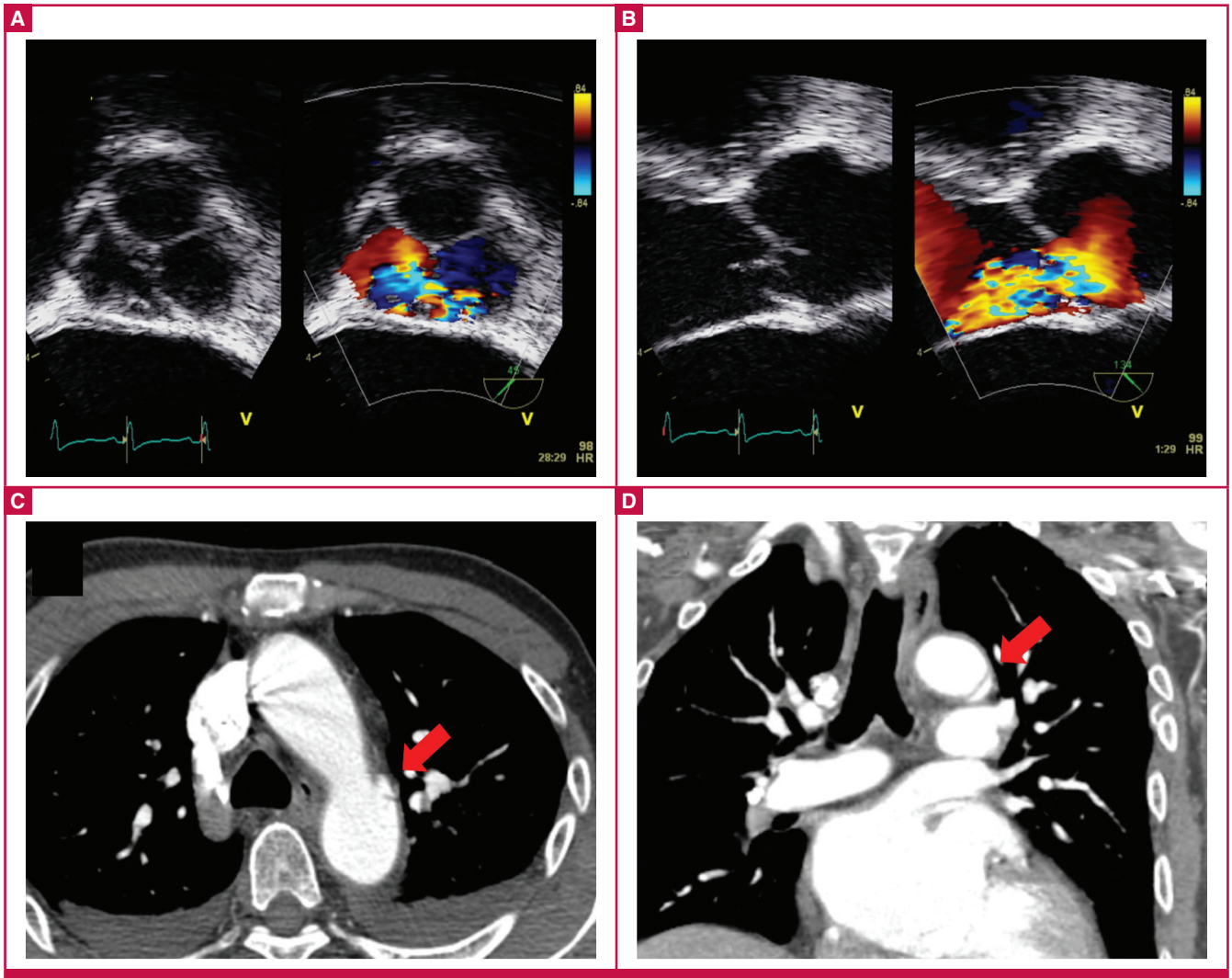

Fig. 1. Aortic regurgitation shown in transoesophageal echocardiography and pseudo-aneurysm seen in computed tomography. (A) In the short-axis view, a tear of the non-coronary cusp was suspected, and in the short-axis view with colour Doppler, significant severe aortic regurgitation in the region of the non-coronary cusp was seen. (B) A long-axis view revealed rupture of non-coronary cusp with torn linear tissue, and in the long-axis view with colour Doppler, severe aortic regurgitation with rupture of the non-coronary cusp was seen. (C) In a post-enhanced axial view, a small pseudo-aneurysm (arrow) in the aortic isthmus is demonstrated. (D) A coronal reformatted image revealed a small pseudo-aneurysm (arrow) at the level of the proximal descending thoracic aorta.

Postoperative echocardiography and computed tomography showed a well-functioning prosthetic aortic valve without regurgitant flow, and a correctly placed stent graft without endoleak. The patient was discharged two weeks after the operation. He remained haemodynamically stable until the discharge. After one month, in an out-patient clinic, the patient showed good functional recovery.

Discussion

Traumatic injury of the aorta is relatively rare, being reported in less than 5% of traumatic vascular injuries. However, the true incidence is likely to be higher, as many victims die prior to hospitalistion for definitive care.[4] Rupture of the aortic valve is extremely rare and there are only a few reports to date. Our patient presented with two different lesions, both from blunt chest trauma; one was a pseudo-aneurysm at the isthmus of the aorta and the other a rupture of the aortic valve.

The mechanism leading to damage of the aortic valve in an accident is suspected to be due to massive increase in intra-thoracic pressure, leading to an increase in intra-aortic pressure. When this occurs during the early diastolic phase, the phase of lower left ventricular pressure, a high pressure difference could develop across the closed aortic valve. This high pressure difference causes aortic valve damage.[2,5,6]

The descending aorta is attached to the chest wall, whereas the heart and great vessels are relatively mobile. Therefore, a traumatic injury of the aorta more frequently involves the descending rather than the ascending aorta.[2,7] Traditional views have been that sudden deceleration causes a tear at the junction between the fixed and mobile portions of the aorta, usually at the aortic isthmus distal to the origin of the left subclavian artery (ligamentum arteriosum).[8]

Injury of the ascending aorta caused by chest wall trauma

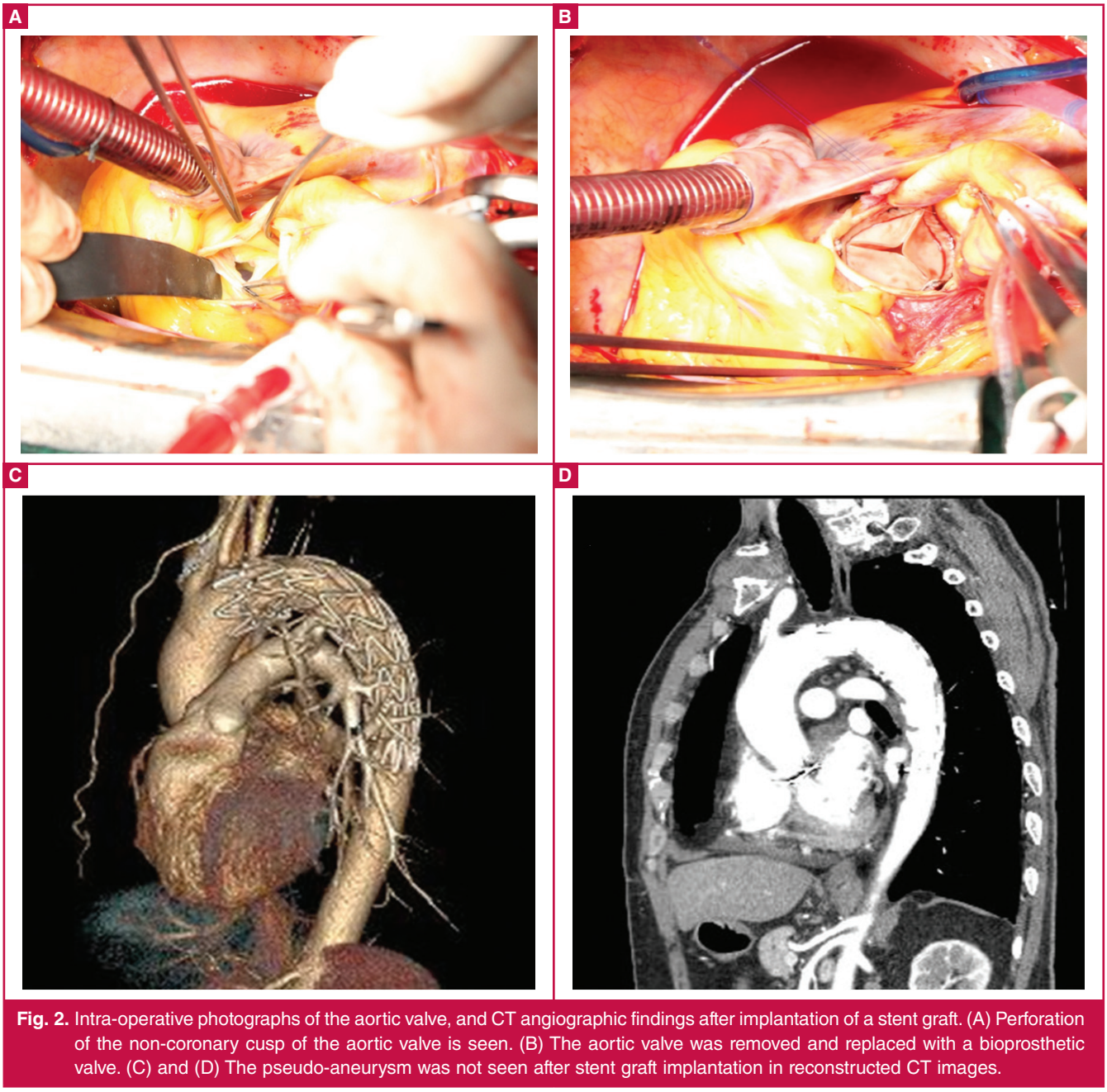

Fig. 2. Intra-operative photographs of the aortic valve, and CT angiographic findings after implantation of a stent graft. (A) Perforation of the non-coronary cusp of the aortic valve is seen. (B) The aortic valve was removed and replaced with a bioprosthetic valve. (C) and (D) The pseudo-aneurysm was not seen after stent graft implantation in reconstructed CT images.

is relatively uncommon and usually fatal. The combination of aortic valve injury and ascending thoracic aorta injury is rare and there are only a few case reports. Furthermore, there are no reports of the combination of aortic valve injury and traumatic pseudo-aneurysm of the aortic isthmus.

The causative mechanism of aortic valve injury is thought to be different from that of injury of the descending aorta.[2] It has been reported that post-traumatic aortic valve regurgitation rather than injury of the descending aorta is often found with sternal or multiple rib fractures. It has been proposed that the impact of a fractured sternum could limit displacement of the heart and ascending aorta during an accident, and this would prevent traction on the aortic isthmus.

When the thoracic wall is fractured, the movement of the heart is restricted by the fractured sternum and a force is exerted on the ascending aorta rather than on the aortic isthmus. This force would affect the column of blood within the aorta, which could rupture the ascending aorta or a valve apparatus but the aortic isthmus would be safe. Therefore, the simultaneous development of both aortic valve injury and descending thoracic aorta rupture by external trauma is unlikely to happen.

The exact mechanism of a combination of aortic valve rupture and traumatic pseudo-aneurysm of the aortic isthmus is not clearly understood. We propose that the pathophysiology of aortic injury after blunt chest trauma could be caused by a variety of mechanisms, not just one.

It is difficult to diagnose aortic regurgitation if a patient has multiple injuries. Echocardiography, history taking, and physical examination are helpful to make a diagnosis. However, making a correct diagnosis my still be challenging since a patient often presents with multiple traumatic injuries from an accident, such as chest wall pain, and rib or other bone fractures.[1] Since a

physician can easily misdiagnose traumatic aortic valve injury, close attention should be paid to patients with blunt chest trauma in clinical settings. In addition, when aortic injuries are detected, thorough examination is needed so as not to miss other possible aortic lesions.

Conclusion

Recently, the hybrid approach as a treatment modality, using surgical and interventional procedures, has been increasing widespread. We decided to use the staged hybrid treatment without re-admission to address this rare and urgent situation. The staged hybrid procedure was a safe, less-invasive and cost-effective treatment for our patient.

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Case Report

Sustained ventricular tachycardia in a patient with isolated non-compaction cardiomyopathy

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Abstract

Isolated non-compaction of the left ventricular myocardium (INVM) was first described in 1984 as an unclassified cardiomyopathy, not being dilated, hypertrophic or restrictive. It is assumed to occur as a result of an arrest in endomyocardial morphogenesis during normal development of the heart. The disease is characterised by heart failure due to systolic and diastolic left ventricular (LV) dysfunction, systemic emboli and ventricular arrhythmias. Echocardiography has been shown to be the method of choice in diagnosis. INVM is a rare congenital cardiomyopathy and only a few cases of this condition have been reported. It is characterised by prominent and excessive trabeculation in a ventricular wall segment, with deep inter-trabecular spaces perfused from the ventricular cavity. We report a case of INVM with ventricular tachycardia induced during electrophysiological study in a 24-year-old female patient with a family history of sudden death.

Keywords: isolated non-compaction cardiomyopathy, cardiomyopathy, ventricular tachycardia, family history, sudden cardiac death

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Non-compaction cardiomyopathy is a congenital pathological disorder that can occur in association with other congenital anomalies, such as pulmonary valve atresia or aortic atresia with intact ventricular septum.[1] It is also an isolated disease without other structural diseases of the heart.[2]

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The incidence of non-compaction cardiomyopathy is estimated at 0.05% in adults. Echocardiography has been shown to be the method of choice in the diagnosis of isolated non-compaction of the left ventricular myocardium (INVM). The age of onset of symptoms ranges from infancy to old age. INVM is the result of an arrest in compaction of the myocardial fibres during intrauterine life. Although the most frequent sites involved are the left ventricular (LV) apex and inferior wall, involvement of other LV walls and the right ventricle has also been reported.[3]

The prognosis of patients with INVM is determined by the degree and progression of heart failure, and the presence of thromboembolic events and arrhythmias. Symptoms of heart failure lead to hospital admission in the majority of adult patients with INVM. Arrhythmias include atrial arrhythmias, ventricular tachycardia, and sudden cardiac death.[4]

Case report

A 25-year-old female came to the out-patient cardiology department with a history of palpitations, sweating and shortness of breath over the previous two months. Her New York Heart Association functional capacity was class II. She mentioned that her mother had died suddenly at 25 years old without any known reason. There was no history of any risk factor for coronary artery disease or any other significant medical illness in our patient.

On physical examination, her pulse rate was 110 beats per minute and blood pressure was 100/60 mmHg. On auscultation, the heart rate was dysrhythmic and tachycardic, and the heart sounds were normal except for a systolic 2/6 ejection murmur heard at the apex. She had mild bilateral pedal oedema. Other examination findings were essentially normal. In addition, laboratory results were within the normal range.

An electrocardiogram showed atrial fibrillation with a rapid ventricular response and non-specific intraventricular conduction delay. On transthoracic Doppler echocardiography, the left ventricle was visualised as hypertrophied and dilated with an end-diastolic diameter greater than 6 cm. LV wall motions were globally hypokinetic and the ejection fraction was calculated as 32% by the Simpson method. There was mild mitral and tricuspid regurgitation.

The echocardiographic findings were suggestive of INVM, with the end-systolic ratio of the non-compacted structure of the left ventricle to the compacted layer greater than 2, prominent trabeculations and deep inter-trabecular recesses, into which blood from the ventricular cavity was flowing, established by colour Doppler (Fig. 1D). The non-compacted segments were

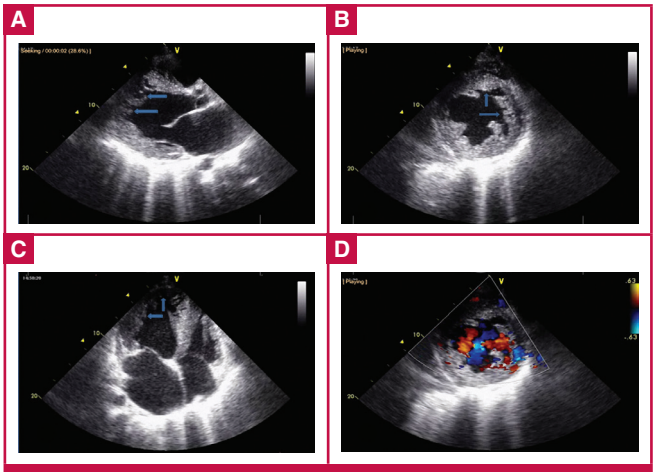

Fig. 1. Transthoracic two-dimensional parasternal long-axis (A), parasternal short-axis (B), and apical four-chamber (C) images show isolated non-compaction of the left ventricle with multiple trabeculae and inter-trabecular recesses in the lateral, apical, anterior and mid-septal areas. Appearance of blood flow from the ventricular cavity to these deep trabeculae was detected by colour Doppler imaging (D).

mainly in the apical, lateral and anterior walls, and mid-septal portions of the left ventricle (Fig. 1A, B, C). There were no co-existing cardiac abnormalities detected.

Non-compacted areas of the left ventricle were easily distinguished from healthy segments by magnetic resonance imaging (Fig. 2A). Coronary angiography revealed normal coronary anatomy. The inter-trabecular recesses in the LV wall were demonstrated by ventriculography (Fig. 2B). In addition, sustained ventricular tachycardia was induced during electrophysiological study (Fig. 3). Medical cardioversion with 1 200 mg iv amiodarone was administered to convert the arrhythmia to sinus rhythm to haemodynamically stabilise the patient.

The patient was put on amiodarone and anticoagulant therapy in addition to optimal heart failure treatment consisting of metoprolol 50 mg, ramipril 2.5 mg, furosemide 40 mg and spironolactone 25 mg po qd. After implantable cardioverter-defibrillator (ICD) implantation, the patient was discharged and advised to continue the treatment. We also recommended echocardiographic evaluation of her first-degree relatives, considering the familial association of INVM.

Discussion

The incidence of non-compaction cardiomyopathy is about 0.05% in adults. Non-compaction of the LV myocardium is the result of an arrest in compaction of myocardial fibres during embryogenesis. It is most frequently observed in the left ventricle but the right ventricle may also be affected. The disorder is diagnosed by two-dimensional echocardiography.[3] Computed tomography and magnetic resonance imaging (MRI) have been reported as useful diagnostic tools in INVM; they may be of value, especially in patients with poor image quality on echocardiography.[5]

The four previously established morphological criteria for echocardiographic diagnosis of INVM is as follows; (1) appearance of at least four prominent trabeculations and deep inter-trabecular recesses; (2) appearance of blood flow from the ventricular cavity into the inter-trabecular recesses as visualised by colour Doppler imaging; (3) the segments of non-compacted myocardium mainly involve the apex and the inferior mid- and lateral mid-LV wall and typically show a two-layered structure with an end-systolic ratio greater than two between the non-compacted sub-endocardial layer and the compacted sub-epicardial layer; and (4) absence of co-existing cardiac abnormalities.[6]

In a study by Jenni *et al.*, the prevalence of non-compacted cardiomyopathy was determined at 0.04% in five years.[7] Ventricular non-compaction was an isolated finding in 74% of the cases and non-compacted ventricular myocardium involving only the left ventricle was 62%. While 77% of patients were in

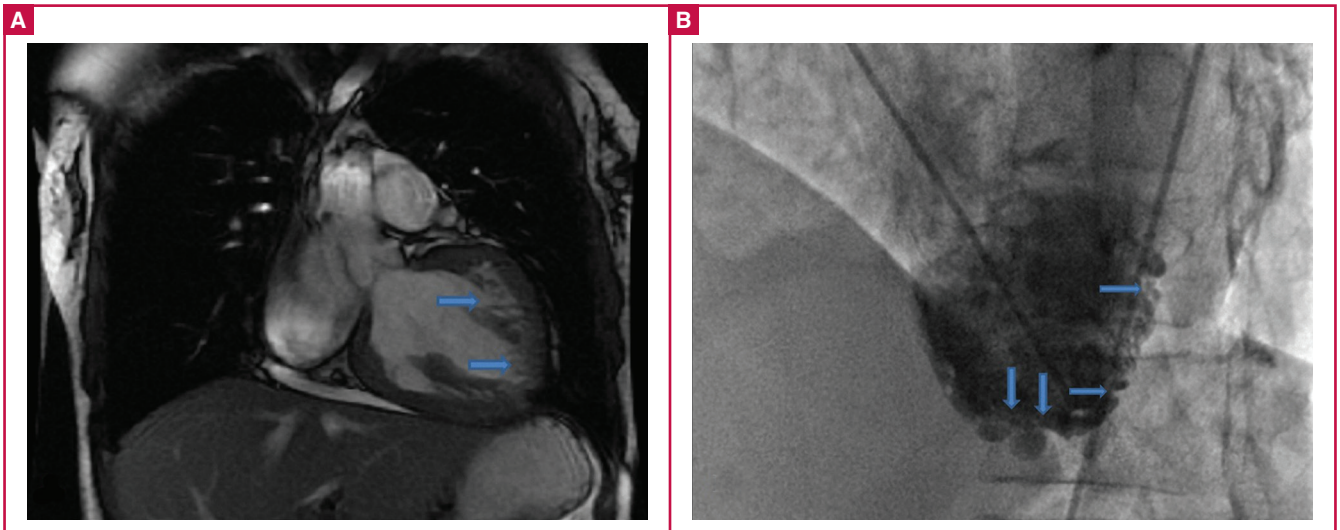

Fig. 2. (A) Multiple deep trabeculae and inter-trabecular recesses of the left ventricle can also be demonstrated by MRI. (B) Left ventriculogram of the patient showing inter-trabecular recesses, especially in the left ventricular apical and lateral wall.

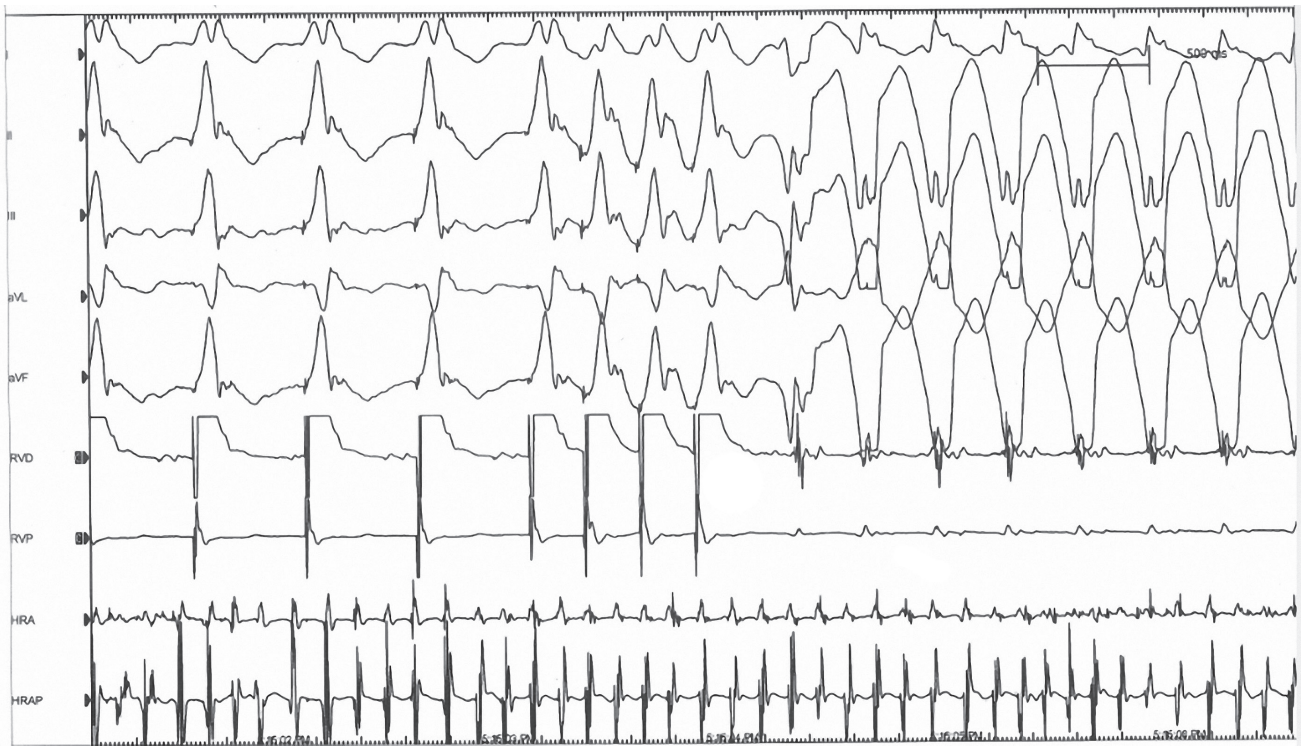

Fig. 3. ECG shows basal atrial fibrillation and sustained monomorphic ventricular tachycardia, induced after programmed ventricular stimulation.

functional class I/II, the remaining had symptoms of congestive heart failure. Ventricular arrhythmias were documented in more than a third of the patients. In this study, the presence of ventricular non-compaction in more than three segments was the sign of a poor prognosis and was associated with a functional class greater than II and ventricular arrhythmias.[7]

In a nine-year echocardiographic study by Ritter *et al*., only 17 cases of INVM in adult subjects were identified.[8] They also emphasised that diagnosis of non-compaction of the LV myocardium in an adult population may be overlooked because of similarities with other more frequently diagnosed cardiomyopathies, and echocardiographic screening of first-degree relatives was recommended due to its familial association.[9]

Kahn *et al.* stated that end-stage congestive heart failure should be managed with heart transplantation, and potential life-threatening ventricular tachyarrhythmias with an ICD because the main causes of death were severe heart failure and sudden cardiac death.[10] In a study by Fazio *et al*. of 238 patients affected by non-compaction, only 11 patients had documented ventricular tachycardia.[11] In another study, it was stipulated that INVM was often related to systolic dysfunction and ventricular dilatation. Malignant ventricular arrhythmias were seen in 47% and sudden cardiac death in almost 50% of the patients.[12] In addition, other cases of INVM, presenting initially with ventricular tachycardia, have been described in the literature.[13,14]

Conclusion

A high index of suspicion for the diagnosis of INVM is necessary because of the high incidence of heart failure and other complications, such as malignant ventricular arrhythmias, death and thromboembolic events. Early diagnosis is important and may be life-saving, especially for patients with a family history of sudden cardiac death, as seen in our case. Treatment should be individualised and directed towards prevention and management of heart failure, ventricular arrhythmias and thromboembolic events.

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Case Report

Coronary artery bypass grafting in a Behçet's disease patient

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Abstract

Behçet's syndrome is a chronic, multisystemic, inflammatory, vasculitic disorder characterised by oral aphta, ocular lesions, genital ulcers and the involvement of other systems. Although vascular involvement is seen frequently, coronary artery disease is extremely rare in Behçet's disease and it is generally treated with invasive or conservative procedures. In this case, we aimed to present a successful bypass grafting of three vessels using cardiopulmonary bypass in a patient with Behçet's disease.

Keywords: Behçet's disease, coronary artery bypass surgery, vasculitis

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Behçet's disease was first defined in 1937 by Hulusi Behçet who was a Turkish dermatologist. It is classified in vasculitic disorders as an autoimmune disease. This disease affects multiple systems including the eye, musculoskeletal, skin, neurological and cardiovascular, with a variety of clinical presentations. Vascular involvement is seen frequently (7–29%) and it is usually related to the venous system. Cardiac involvement is extremely rare (0.2%).[1]

Arterial system involvement is rarely seen compared to the venous system. Thrombus formation, pseudo-aneurysm, stenosis and occlusion can be seen in the arterial structures and these may be fatal. In Behçet's disease, endothelial function is affected to varying degrees, and additionally, patients are prone to hypercoagulation, caused by activated endothelial cells and platelets.

Little is known about the origin of the inflammatory obliterative endarteritis, endothelial cell activation and perivascular mononuclear cell infiltration, which cause damage to the vascular media and deterioration in the arterial and venous structures. Aneurysm formation is frequently seen, however, stenosis and oclusions caused by endothelial damage and hypercoagulation are rarely seen.[2]

Involvement of the coronary arterial system is extremely rare in Behçet's disease and these patients are generally treated conservatively. The number of patients undergoing coronary artery bypass grafting (CABG) is low because these tissues become fragile, vascular structures are destroyed and hypercoagulation is frequent in these patients.[3,4] The grafts that are used for CABG surgery may be affected by the disease and this is related to long-term failure.

Behçet's disease is a chronic autoimmune vasculitis and patients are commonly on immunsupresive therapy before surgery. This is also a risk for surgery and postoperative survival.

For these reasons, the decision to operate is controversial. Surgeons generally avoid surgical manipulation as much as possible. When CABG is inevitable, minimally invasive procedures would be prefered. If cardiopulmonary bypass is absolutely necessary, the surgeon must be mindful of these risks.

Case report

A 53-year-old man, whose Behçet's disease was diagnosed 30 years earlier, had been on colchicine therapy since then. He had had deep venous thrombosis in his left leg three years previously, and had been using azathioprine for three years.

He complained of a burning in the midline of his chest for the last year and had no cardiac risk factors (e.g. smoking, diabetes mellitus, dyslipidaemia, hypertension) except Behçet's vasculitis. There was no pathology on colour Doppler ultrasonography, and pulmonary computed tomography was normal. Coronary angiography was performed and the decision was made to perform CABG because he had significant stenosis in the proximal left anterior descending (LAD), diagonal and right coronary arteries.

The left internally mammary artery (LIMA) was anastomosed to the LAD using cardiopulmonary bypass (CPB). Diagonal and right coronary anastomoses were performed using saphenous vein grafts. All tissues were very fragile so we had to be careful with manipulation and the control of bleeding.

The surgery was non-problematic. On the first day after the operation, 850 cm^3 blood from the chest tubes was detected and followed up. There were no other complications. We did not use an anticoagulant, only antiplatelet therapy (300 mg/day aspirin). The chest tubes were removed on the fifth day. The patient was

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discharged without problems on the 10th postoperative day, with oral prednisolone, colchicine, azathioprine, a beta-blocker and aspirin. The one-year follow up was uneventful.

Discussion

Most clinical findings in Behçet's disease are related to vasculitis, and arterial disease is commonly seen as small-vessel involvement. Acute myocardial infarction caused by coronary artery vasculitis may be seen but this is extremely rare. However, Behçet's disease is known to accelerate atherosclerosis, as with another autoimmune disease, systemic lupus erithematosus.

Aneurysm formation is the most common manifestation in the arterial system but stenosis or occlusion may be seen in the coronary vessels, caused by fibrous intimal thickening and localised vasculitis. Coronary arterial disease is generally treated with either conservative or invasive procedures. CABG is very rarely performed.

Some surgeons prefer not to perform CABG because the tissues are fragile, the grafts are affected by inflammation, and hypercoagulopathy may be a problem peri-operatively.[5] Others recommend percutaneous interventions (PCI) or minimally invasive procedures such as off-pump techniques.[6] In our patient, LIMA-to-LAD anastomosis and two saphenous grafts for the diagonal and right coronary arteries were used with cardiopulmonary bypass procedure. Coronary arterial disease in this patient was adversely affecting the quality of his life and the lesions were not amenable to PCI or stent use.

Major problems after surgery are bleeding and anastomotic pseudo-aneurysm. Minimal manipulation of the tissues, taking care of bleeding peri-operatively and the use of corticosteroids are important for these severe complications. For this reason, we prefered oral steroids for our patient after surgery.

Another problem in Behçet's disease is haematoma/pseudo-aneurysm, including the femoral artery after coronary angiography. Multiple punctures should be avoided and catheters should be removed as soon as possible to prevent these complications. We removed all the catheters on the first postoperative day.

There is uncertainty about whether the coronary lesions are caused by atherosclerosis or vasculitis in these patients. Also, there are no comprehensive studies on the long-term patency of the grafts used for coronary bypass in Behçet's disease because the grafts may be affected by the disease. There is a need for these kinds of studies involving large numbers of patients.

Conclusion

Behçet's disease involves all types of vessels but coronary arterial involvement is extremely rare. The patients are generally young and they are frequently treated medically. CABG is very rarely performed on these patients and off-pump techniques are generally prefered. In our opinion, when CABG is necessary, minimal manipulation of the tissues, careful choice of grafts, awareness of thrombosis and other peri/postoperative complications are very important for these patients.

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