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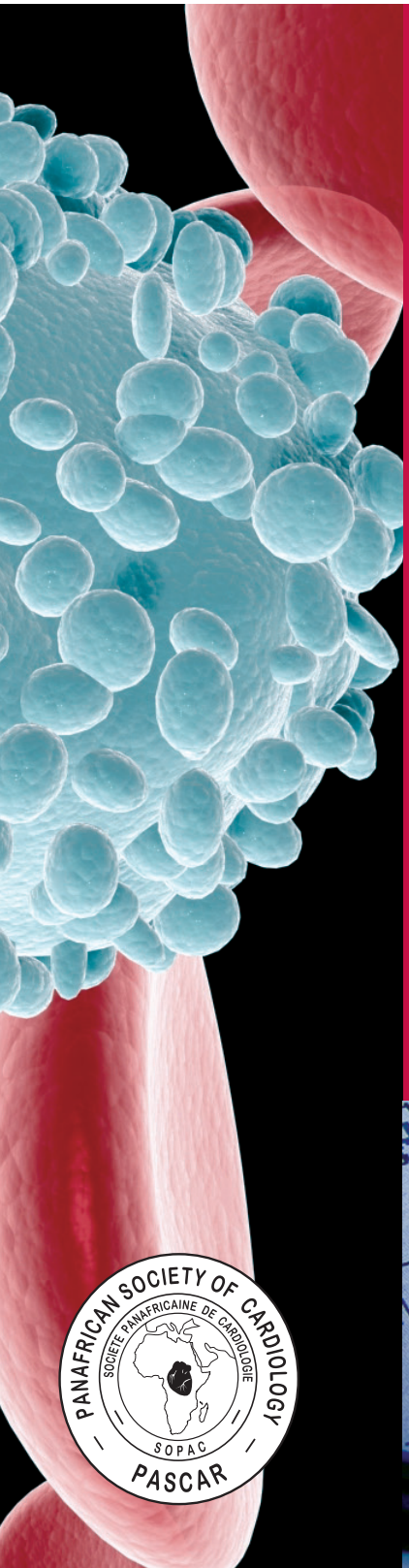

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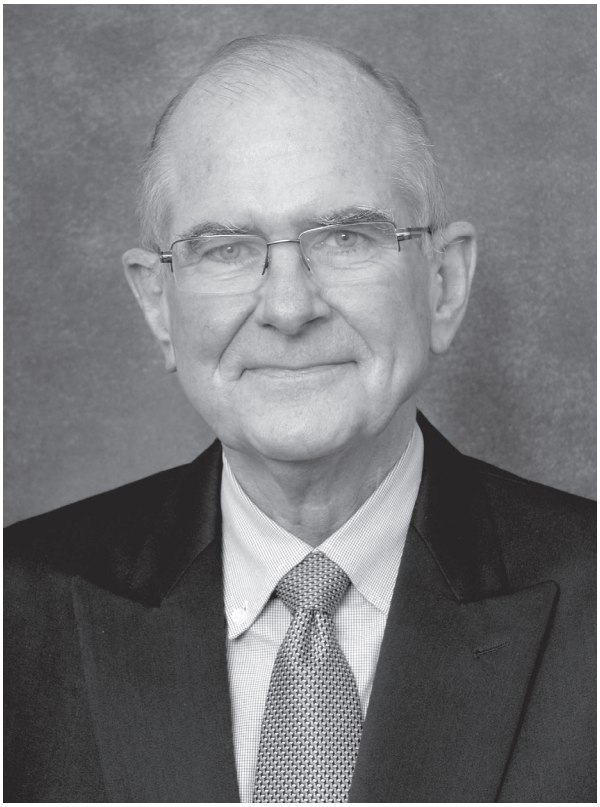
From the Editor's Desk

Healthcare professionals often label patients as 'non-compliant' when prescribed therapies seem to fail to be effective. This is often used as a derogatory term of criticism of patient behaviour, as though patients are personally liable for their lack of response and continued ill health. Those of us who have experienced having been prescribed long-term medication, requiring multiple daily doses, will readily admit to the difficulty of complying fully with complex regimens despite the best will in the world. The article by Osamor in this issue (page 29) explores the importance of social support in the management of a chronic disease in Africa and confirms the importance of such support in ensuring compliance with prescribed medication. Given the evidence from elsewhere that familial and social support is of importance in lessening the likelihood of developing cardiovascular disease and increasing the likelihood of compliance with treatment, the results are not surprising, and are important for those teaching medicine and planning treatment programmes in Africa. Hopefully the results will stimulate further African research in this important area.

Coronary artery bypass grafting (CABG) has produced excellent symptomatic relief from angina for many patients and enhanced survival in selected sub-groups. Symptomatic relief is inevitably time-limited by durability of the venous conduits. When symptoms recur due to vein graft failure and a percutaneous intervention is not feasible, patients and clinicians face a difficult dilemma, particularly if there is a patent left internal thoracic artery anastomosis to the left anterior descending coronary artery that may be jeopardised at the time of repeat median sternotomy. Such patients are inevitably older with multiple co-morbidities. Duvan and colleagues (page 25) report their experience with redo off-pump CABG via a posterolateral thoracotomy to access branches of the circumflex coronary artery. This report serves as a timely reminder of an alternative revascularisation strategy that may well be acceptable to both patients and referring cardiologists when severe symptoms persist despite optimal medical therapy.

The precise relationship between obesity and coronary disease remains unclear. Zand-Parsa and colleagues (page 13) add a new level of complexity by demonstrating that obesity, as determined by waist-to-hip ratio (WHR), was correlated with severity of coronary artery disease by two independent scoring systems, whereas body mass index (BMI) was not. Clinicians will be aware of considerable ethnic variation in patterns of distribution of adipose tissue and this is not always considered in comparisons of BMI and WHR. It may, in part, account for some discrepancies, and the establishment of regional norms may be necessary.



Professor PJ Commerford

Laboratory experimental work by Burma (page 4), using pre-constricted internal mammary artery (IMA) rings in a tissue bath, showed that leptin caused relaxation of these arterial segments. These findings led the authors to raise the intriguing hypothesis that obese subjects who had a left IMA bypass graft would actually have better (anterior wall) myocardial perfusion compared to non-obese subjects. The risks and benefits of obesity in patients with coronary disease are far from settled!

PJ Commerford
Editor-in-Chief

Cardiovascular Topics

In vitro effects of sodium nitroprusside and leptin on norepinephrine-induced vasoconstriction in human internal mammary artery

Oktay Burma, Mete Ozcan, Emine Kacar, Ayhan Uysal, Engin Şahna, Ahmet Ayar

Abstract

Aim: The biological and pharmacological properties of vessels used in coronary artery bypass graft (CABG) surgery are as important as their mechanical properties. The aim of this study was to investigate the possible role of protein kinase C (PKC)-dependent mechanisms in leptin-induced relaxation in the human internal mammary artery (IMA).

Methods: IMA rings, obtained from patients undergoing CABG surgery, were suspended in isolated tissue baths containing Krebs-Henseleit solution, which were continuously gassed with 95% O_2 and 5% CO_2 at 37°C.

Results: The IMA rings were pre-contracted with increasing concentrations of norepinephrine (NE 10^{-9}–10^{-4} mol/l) and the relaxation responses to sodium nitroprusside (SNP), a nitrosovasodilator, and leptin were studied in the presence and absence of a PKC inhibitor. Leptin (1 µM) caused a dose-dependent relaxation in NE pre-contracted IMA rings. Pre-treatment with a PKC inhibitor significantly attenuated this vasorelaxatory response to leptin in human isolated IMA.

Conclusion: It was found that SNP and leptin caused significant relaxation of the NE pre-contracted human IMA rings, and PKC was probably the sub-cellular mediator for this effect. Our findings may have clinical or pharmacological importance as it could be hypothesised that obese subjects who have a left IMA bypass graft would have better myocardial perfusion.

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Coronary heart disease (CHD) and stroke are the largest contributors to global mortality in low-, middle- and high-income countries as a result of current lifestyles. They will continue to cause decreased quality of life and contribute to the causes of morbidity and mortality throughout the world.[1,2]

CHD, also known as coronary artery disease, is the narrowing of coronary arteries, hampering blood and oxygen supply to the heart when plaque builds up in the arteries. The heart is an aerobic organ and disruption of its normal oxygen supply causes irreversible changes in heart tissue. If the disruption of oxygen supply is severe, this becomes life threatening.[3]

Although CHD cannot be cured, there are several treatment options to relieve the symptoms and reduce the progression and risk of complications (heart attack), and thereby prolong the expected lifespan. Treatment options include lifestyle changes and medication, but depending on the severity of the disease, more aggressive treatment methods including interventional procedures (angioplasty and stenting) or coronary artery bypass surgery are warranted.[4]

Revascularisation by coronary artery bypass graft (CABG) surgery is a process of restoring the blood flow around existing blockages to the heart using autologous bypass grafts (or artificial grafts). The immediate success of this procedure is related to surgical technique and the anatomical characteristics of the grafted coronary artery.[5] After grafting, the vascular smooth muscle cells of the new vessels are the primary regulators of vascular tone. Therefore characterisation of the contractile and relaxatory profiles of the commonly used graft vessels in response to major coronary vasodiladator and vasoconstrictor agents has been carried out in *in vitro* pharmacological investigations.

The effects of noradrenaline, dopamine,[6] adenosine and nitric oxide[7,8] are well established, but other endogenous agents[9] that increase in concentration in the circulation during cardiovascular disease are poorly studied. Leptin is a hormone secreted mostly from adipocytes, which is also produced in small amounts from

other human tissues such as the heart, stomach, placenta and mammary epithelium.[10-14] In addition to its essential roles in feeding behaviour and energy balance,[11,12] leptin also plays an important role in many different peripheral processes, including haematopoietic, nociception, reproduction, immunity, wound healing, bone remodelling and cognitive functions.[13]

The internal mammary artery (IMA) is the most commonly used vessel in coronary artery grafting to bypass stenosed coronary arteries. Morever its patency rate is longer lasting than the saphenous vein (SV). The IMA has a dynamic vascular bed therefore several vasoactive substances may cause contractile or dilatory responses in the IMA.

Protein kinase C (PKC) is a family of serine/threonine protein kinases. It plays a critical role in the pathogenesis of many heart diseases.[15-17]

Although it has been documented that leptin has a vasodilatatory effect,[18,19] the cellular mechanism of this effect is not well documented. The aim of this study was to investigate the possible involvement of PKC-mediated mechanism(s) in the vasorelaxatory effects of sodium nitroprusside (SNP) and leptin on norepinephrine pre-contracted excised human IMA.

Methods

Informed consent was obtained from the patients and the Clinical Research Ethics Committee of Firat University Medical Faculty (Elazig, Turkey) approved the use of discarded human IMA segments in this study. Segments of the left IMA were collected from 20 patients undergoing CABG. Demographic and clinical characteristics of these patients are given in Table 1.

The IMA were carefully cleaned of loose connective tissue and cut into rings (about 2–3 mm long). The preparations were placed in an isolated tissue bath containing Krebs-Henseleit (KH) solution (composition in mM: NaCl 118, KCl 4.7, $MgSO_4$ 1.2, $CaCl_2$ 1.25, KH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11, EDTA 0.03) at 37°C and pH 7.4, constantly bubbled with a mixture of 95% O_2 and 5% CO_2. Contractile activities were recorded using a physiological force transducer (FDT05, Commat Ltd, Ankara, Turkey) recorded by MP150WS for Windows (Biopac Systems Inc, CA, USA).

Table 1. Some clinical features of 20 patients undergoing CABG

Clinical features	*Mean ± SD,* n *(%)*
Age	66.5 ± 8.0
Weight	73.2 ± 8.5
Body mass index	27.8 ± 2.6
Gender	
Male	12 (60)
Female	8 (40)
Smoking	9 (45)
Diseases	
Hypertension	17 (85)
Heart failure	3 (15)
Diabetes	10 (50)
Medication	
Organic nitrates	0 (0)
Aspirin	20 (100)
Beta-blockers	14 (70)
Angiotensin inhibitors	9 (45)
Calcium channel blockers	5 (25)
Hypolipidaemics	13 (65)

At the beginning of the experiments, the resting tension of the IMA vessels was adjusted to 1 g and they were allowed to equilibrate under this resting tension for 120 min. Following a stabilisation period, cumulative concentrations of norepinephrine (NE) (10^{-9}–10^{-4}M) and SNP (10^{-9}–10^{-4}M) were applied to the organ bath to determine the concentration for a maximum response.

Leptin, NE and SNP were obtained from Sigma (St Louis, MO, USA). The PKC inhibitor, chelerythrine chloride, was obtained from Tocris Bioscience. Each stock solution was diluted to the required concentration immediately before bath application.

Statistical analysis

Data are presented as mean ± SD. The effects of leptin (1 µM) on contractile activity were evaluated using the unpaired Student's *t*-test. For all analyses, $p < 0.05$ was regarded as significant.

Results

The effects of leptin (1µM) and SNP (10^{-9}–10^{-4}M) on the NE concentration (10^{-9}–10^{-4}M) that evoked maximal contractile responses in human IMA rings were studied. The ability of the PKC inhibitor, chelerythrine chloride, to modulate the contractile activity to leptin was also examined.

Firstly we tested the effects of leptin on basal tension. Treatment with leptin (1 µM) did not cause any significant change in basal tension of the IMA rings (data not shown). Cumulative concentrations of NE elicited dose-dependent contraction of the IMA rings. This contractile response was repeatable without any significant run-down (data not shown).

In different protocols, the effects of leptin on dose-dependent contractile responses to cumulatively added NE (10^{-9}–10^{-4}M) were observed. The contractile responses to NE were significantly attenuated by the addition of leptin (1 µM, Fig. 1A, $p < 0.05$, $n = 20$). Cumulatively added SNP-induced vasodilatation (10^{-9}–10^{-4}M) was also significantly attenuated by leptin (1 µM) (Fig. 2, $p < 0.05$, $n = 20$).

Furthermore, as can be seen in Fig. 1B, 10 µM chelerythrine chloride caused a significant attenuation of vasodilatator response to leptin (Fig. 2, $p < 0.05$). PKC-mediated signalling pathways were probably involved in the leptin-induced vasoactive responses in the human IMA rings.

Discussion

In the present study, we examined the effects NE, SNP and leptin in isolated human IMA rings. In agreement with the literature and from our clinical results, application of NE to IMA rings caused a dose-dependent contraction. Subsequent application of SNP caused a dose-dependent relaxation. Addition of leptin interrupted the endothelium-independent relaxatory effect of SNP, attenuating its relaxatory effect. Leptin alone did not cause any change in the basal tension of the IMA segments but caused significant relaxation of the NE-induced contractile activity. This is the first study to show that leptin provided a relaxatory effect on the NE-induced contraction of isolated IMA segments, and this effect was PKC dependent.

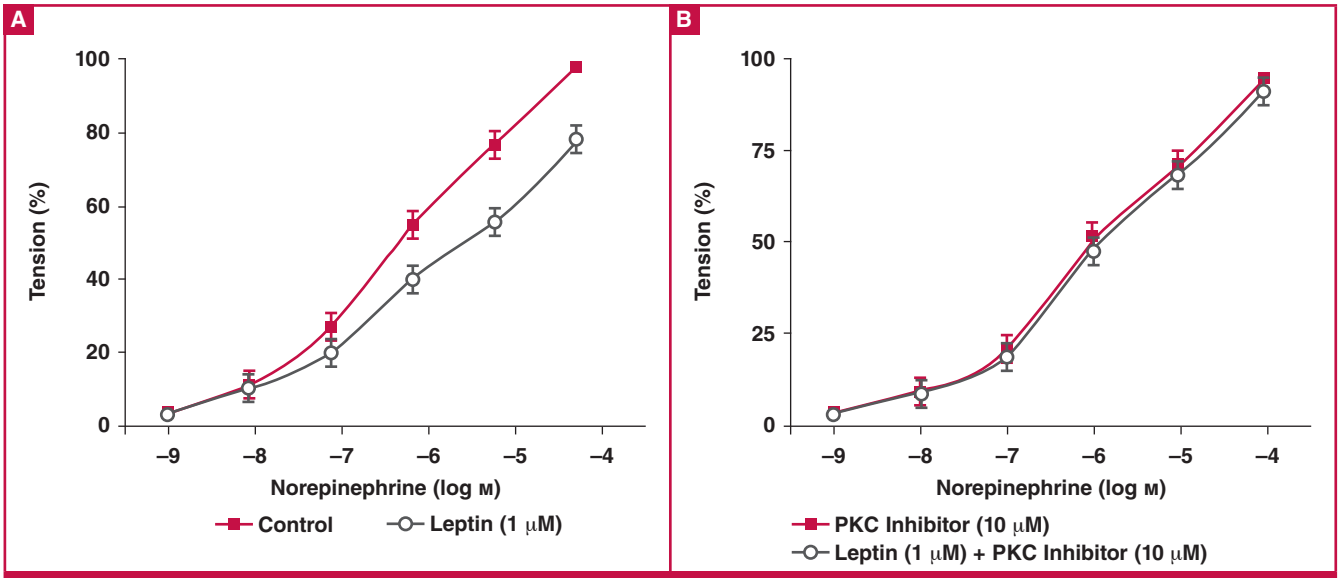

Fig 1. Effects of leptin on sodium nitroprusside-induced relaxation response in norepinephrine pre-contracted human internal mammary artery rings in the absence (A) and presence (B) of chlerythrine chloride (PKC inhibitor).

As presented in Table 1, IMA rings were obtained from a range of patients undergoing CABG surgery due to various cardiovascular diseases. Although most of the associated risk factors have been shown not to affect endothelium-dependent contractile responses of the arteries from these patients,[20] and both endothelium and smooth muscle are affected by risk factors, we chose to use endothelium-independent relaxation protocols.

The finding of SNP-induced (endothelium-independent) relaxation of the IMA rings indicated that possible injury to the endothelium during harvesting and/or grafting does not totally impair the relaxation capacity of this conduit artery. The contractile functionality of coronary artery grafts has been a topic of substantial interest and has been studied extensively in different vessels, including human saphenous veins, radial artery and IMA.[21-24]

Leptin has been shown to cause endothelium-dependent vasorelaxation of the peripheral arteries of experimental animals.[25] Leptin has also been shown to exert an endothelium-independent vasodilatory action in humans with coronary artery disease.[26] Therefore, in addition to its central role in the regulation of energy balance and metabolism, leptin has direct effects on the blood vessels (atherogenic, thrombotic and angiogenic) of both coronary and cerebral arteries, potentially contributing to the progression of atherosclerosis in the coronary vessels.[27-29]

Conclusion

By investigating the mechanism and effect of leptin on NE pre-contracted IMA segments, a vessel commonly used for CABG, our *in vitro* study has provided further pharmacological evidence on the characteristics of this vessel. Leptin induced direct vasodilatation of the IMA, and PKC was potentially a sub-cellular mediator for the leptin-induced vasodilatation of these arteries. Although the physiological function of leptin

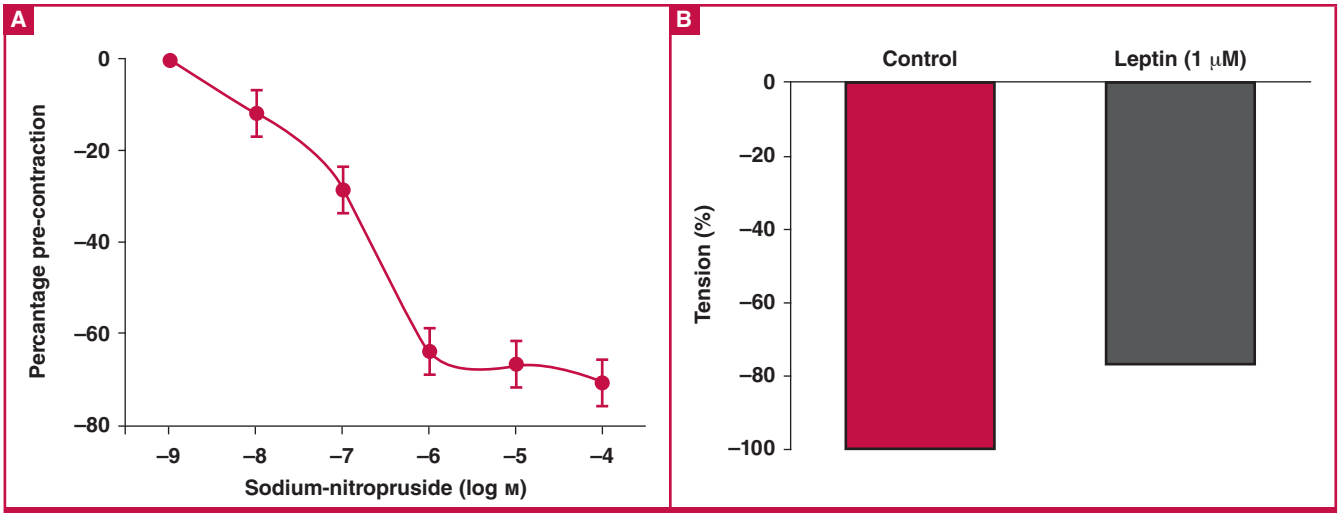

Fig 2. Effects of leptin on sodium nitroprusside-induced relaxation in norepinephrine pre-contracted human internal mammary artery rings. The magnitude of the relaxation response is expressed by tension bars.

is rather contradictory, as it is associated with left ventricular hypertrophy in hypertensive, insulin-resistant men, it also induces direct vasodilatation through distinct endothelial mechanisms. Our findings therefore may have clinical or pharmacological importance. In the light of these findings, it could be hypothesised that obese subjects who had a left IMA bypass graft would actually have better (anterior wall) myocardial perfusion compared to non-obese subjects. There is a need for further studies investigating possible differences in IMA responses to leptin in vessels from patients with different body mass indexes.

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Abdominal aortic stiffness as a marker of atherosclerosis in childhood-onset asthma: a case–control study

Zülal Ülger, Figen Gülen, Arif Ruhi Özyürek

Abstract

Background: Asthma is one of the chronic inflammatory diseases. It is known that chronic inflammation accelerates atherosclerosis. Abdominal aortic stiffness parameters can be used to detect the early development of atherosclerosis.

Aim: In this study, we aimed to evaluate abdominal aortic stiffness parameters in childhood-onset asthma compared with a control group.

Methods: In this cross-sectional, case–control study, we evaluated 50 patients with childhood-onset asthma, and 57 healthy children as controls. Patients with a diagnosis of asthma of at least three years' duration were included in the study. Children with hypertension, hyperlipidaemia, diabetes, a history of smoking contact, or systemic disease were excluded. The study and control groups were evaluated with transthoracic echocardiography, and abdominal aorta diameters were measured. Using the measured data, abdominal aortic stiffness parameters (aortic distensibility: DIS, aortic strain: S, pressure strain elastic modulus: Ep, and pressure strain normalised by diastolic pressure: Ep*) were calculated. Statistical evaluation was done with the Student's t-test, chi-squared test and Pearson's correlation test.

Results: The study group consisted of 50 children (24 female, 26 male) with asthma. According to the GINA guidelines, 26 of the patients had mild intermittant asthma, six had mild persistent asthma and 18 had intermediate persistent asthma. None of the patients had severe asthma. In 37 of the asthma patients, spIgE was positive and these patients were accepted as having atopic asthma; 27 of these patients received immunotherapy. We did not detect any differences between the study and control groups in terms of gender, age and body mass index. No differences were evident between the groups with regard to systolic and diastolic blood pressure, heart rate, blood cholesterol levels and respiratory function test parameters. There was no difference between the asthma and control groups in the measurement of abdominal aortic stiffness parameters. There was no significant correlation between aortic stiffness parameters and high-sensitivity C-reactive protein, blood total cholesterol, LDL cholesterol and HDL cholesterol levels.

Conclusion: We did not find any difference between the asthma patients and control group with regard to aortic stiffness parameters (DIS, S, Ep and Ep*) and there was no difference in these parameters when we compared patients with mild asthma with those with moderate asthma. These results may be due to the anti-inflamatory effect of inhaled steroids. Further studies are needed to validate these results.

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Asthma is an important health problem in children. Substantial evidence has demonstrated that asthma is a chronic inflammatory disease with activation of the inflammatory cells within the airways. Recent studies have reported that systemic inflammation is related to disease progression in asthma.[1] The pro-inflammatory cytokines such as tumour necrosis factor alpha (TNFα), interleukin 6 (IL-6) and C-reactive protein (CRP) are elevated in patients with asthma.[1-3]

Atherosclerosis and asthma are both chronic inflammatory conditions. Inflammation leads to impairment of endothelial cell function, and chronic inflammation accelarates atherosclerosis.[4] Elevated arterial stiffness, a marker of subclinical atherosclerosis, is associated with myocardial infarction, heart failure, stroke, renal disease and elevated total mortality rates.[5]

Much research has revealed that patients with asthma are at increased risk of pulmonary embolism, hypertension, coronary heart disease and heart failure.[6-9] Reduction in arterial distensibility leads to increased pulse pressure, and impedance of arterial flow and pulsatile cardiac work load. Arterial stiffness is a mechanical property related to vascular impedance and the afterload that is presented to the left ventricle. Abdominal aortic stiffness increases with age, and in many studies, its usefulness has been demonstrated.[10-15]

In the literaure, changes in abdominal aortic stiffness in childhood-onset asthma have not been clearly determined. The purpose of our study was to evaluate abdominal aortic stiffness in patients with childhood-onset asthma.

Methods

Our study was a cross-sectional, case–control study. Fifty asthma patients (24 girls, 26 boys) aged eight to 17 years, who were followed by the paediatric allergy department of our hospital for at least three years, were included in this study. Children with hypertension, hyperlipidaemia, diabetes, a history of smoking contact and systemic disease were excluded. The asthma diagnosis was established from a history of intermittent wheezing, the presence of reversible airway obstruction and at least 12% improvement in forced expiratory volume in one second (FEV1) following bronchodilator administration.

The Global Initiative for Asthma guidelines (GINA) was used to determine clinical severity of the asthma.[16] Twenty-six patients had mild intermittant asthma, six had mild persistent and 18 had moderate persistent asthma. Allergen sensitivity in the asthma

patients was determined with specific IgE (sIgE) and skin-prick tests to aero-allergens.

sIgE levels were determined with the CAP FEIA method (Pharmacia, Uppsala, Sweden), which detects sensitisation in the serum against inhaled allergens (wild grass, house dust mite, animal dander, yeasts, grass pollen, trees). The result was considered positive if the measured value was greater than 0.35 kU/l.

The skin-prick test (SPT) was done using Allergopharma (Joachim Ganzer KG, Reinbeck, Germany) commercial allergen solutions. A total of 44 different allergens consisting of house dust mite, grass, wild grass, tree pollens, fungi, animal dander and insects were tested and children with at least one positive test were considered atopic. Asthma patients who had a positive sIgE and sensitivity against at least one aero-allergen on the SPT were included in the atopic asthma group.

Immunocompromised patients, patients with a history of chronic inflammation/rheumatological disorders, diabetes, hypertension, hypercholesterolaemia and those with autoimmune diseases or a history of smoking exposure were excluded. Asthma patients with an exacerbation of their asthma within the previous month or with symptoms of respiratory tract infection were also excluded.

The control group consisted of 57 gender- and age-matched healthy children. They were chosen from children referred to the paediatric cardiology out-patient clinics due to innocent murmur. The control group was evaluated with regard to familial and personal history of hyperlipidaemia and atopy, chronic and/or severe infections, and rheumatological and autoimmune diseases. Children were included in the control group if they had no sign of atopic diseases and no personal familial history of atopy. The control group was also selected from non-smoking households.

The local ethics committee approved the study. Informed consent was obtained from the parents of all subjects in the study and control groups.

The patients in the study group and the healthy controls were weighed with an electronic digital scale that was sensitive to 0.1 kg. Body height was measured and body mass index (BMI) was calculated with the formula: weight (kg)/height^2 (m^2).

A detailed medical history was obtained and a physical examination was performed by the same paediatric cardiologist. Blood pressure was recorded and all subjects were evaluated with a respiratory function test.

Plasma lipid levels were measured after 12 hours of fasting. Serum total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels were measured with Alcyon 300 (Abbott Laboratories, USA) equipment by enzymatic methods. High-sensitivity C-reactive protein (hs-CRP) levels in the study and control groups were measured on an automatic analyser, based on the turbidimetry method.

Blood pressure measurements were done after 15 minutes of rest; the right brachial artery pressure was measured by sphygmomanometer with an appropriate cuff. Both systolic (Ps) and diastolic blood pressure (Pd) were measured, and after three measurements the mean value was obtained. Pulse pressure (PP) was calculated as PP = Ps – Pd.

All the patients and control group underwent two-dimensional, M-mode and Doppler studies using GE Vingmed Vivid 7-model echocardiography (GE Vingmed, Ultrasound AS, Horten, Norway) with a 3-MHz transducer. All the subjects were at rest and lying in the left decubitus position during the examination.

End-diastolic left ventricular posterior wall thickness (LVPWTed), left ventricular end-diastolic and systolic diameters (LVED, LVES), left atrial diameter (LA) and aortic anulus diameters were measured. The ejection fraction (EF) and fractional shortening (FS) were measured from M-mode echocardiographic tracings. The measurements were determined with standard techniques in accordance with the recommendations of the American Society of Echocardiography.[17] Mean pulmonary artery pressure of all subjects was calculated from pulmonary artery accelaration time.

A long-axis view of the abdominal aorta of the subxiphoid area was recorded and maximum systolic (Ds) and minimum diastolic diameter (Dd) was measured by M-mode echocardiography. All echocardiographic measurements were done by the same experienced paediatric cardiologist and intra-observer variability was evaluated with intraclass correlation coefficient (ICC); ICC was 0.9 (excellent reliability).

All aortic measurements were made as previously described by Lacombe *et al.*[10] Aortic strain (S) was calculated from the changes in aortic diameter, and pressure strain elastic module was also calculated from the aortic strain and the changes in brachial artery systolic and diastolic pressure using the formulae: S = (Ds – Dd)/Dd and Ep = (Ps – Pd)/S.

Pressure strain normalised (Ep*) by diastolic pressure was calculated with the equation: Ep* = Ep/Pd. Aortic distensibility (DIS) was calculated according to the previously proposed and evaluated equations[10-15] as: DIS = [2(Ds – Dd)/Dd(Ps – Pd)] × 10^{-6} cm/dyne.

S and DIS represent the distensibility or elasticity of the aortic wall; Ep and Ep* represent the stiffness of the aortic wall, and Ep and Ep* are the mean stiffness of the aorta. S and Ep* are dimensionless ratios, whereas Ep has a dimension and is represented with the unit of N/m^2 (force/unit area).

Statistical analyses

All statistical analyses were performed using Systat statistical software (version 15.0 for Windows; SPSS Inc, Chicago, IL, USA). Data were tested for homogeneity of variance with the Shapiro–Wilk test. The Student's *t*-test (unpaired) and chi-squared test were used for comparison of statistical difference between the groups. Correlations with the aortic elasticity parameters were evaluated with Pearson's correlation test. Statistical significance was taken as $p < 0.05$. All data were presented as mean ± SD.

Results

The study group consisted of 50 children (24 female, 26 male) with asthma. According to the GINA guidlines, 26 of the patients had mild intermittant asthma, six had mild persistent and 18 had intermediate persistent asthma. None of the patients had severe asthma. In 37 of the asthma patients, sIgE was positive and these patients were accepted as the atopic asthma group; 27 of these patients received immunotherapy.

The mean age of the asthma group was 11.7 ± 2.7 years and of the control group, 12.3 ± 2.8 years (34 female, 23 male). There was no difference between the groups in terms of age, gender and BMI

(Table 1). No differences were evident between the groups in terms of systolic/diastolic blood pressure, heart rate, blood cholesterol levels and respiratory function test parameters (Table 1).

Asthma patients and the control group were evaluated with transthoracic echocardiography. There was no significant difference between the two groups in the measurements of LVPWTed, LVED, LVES, IVSed, LA, aortic anulus diameter, EF and FS (Table 2). Mean pulmonary pressure (mPAP) of the asthma patients was higher than in the control group (19.9 ± 7.1 vs 12.6 ± 6.2 mmHg) and this difference was statistically significant ($p < 0.05$). There was no correlation between mPAP and aortic stiffness parameters (Pearson's correlation analysis).

In 15 of the asthma patients, echocardiography revealed mild tricuspid regurgitation and right ventricular systolic pressure was calculated from regurgitant flow. Average right ventricular systolic pressure of these 15 patients was 27.2 ± 5.7 mmHg. Since we had evaluated only asthma patients without exacerbation of their asthma within the previous four weeks, there was no difference in baseline respiratory function test parameters between the study and control groups.

There was no significant difference between the asthma and control groups in the measurements of Ds, Dd, DIS, S, Ep and Ep* (Table 3). There was no significant correlation between aortic stiffness parameters and serum total cholesterol (r = 0.03), LDL cholesterol (r = 0.09), HDL cholesterol (r = 0.09) and triglyceride (r = 0.134) levels (Pearson correlation analysis). There was no correlation between hs-CRP and aortic stiffness parameters, DIS (r = 0.268), Ep (r = 0.199), EP* (r = 0.150) and S (r = –0.230).

Out of 50 asthma patients, 18 had intermediate severity asthma. Aortic stiffness parameters were compared between these patients and the control group. There was no statistically significant difference between the two groups ($p > 0.05$) (Table 4).

Twenty-six of the asthma patients were intermittently using inhalers with short-acting beta-agonists; 10 were also using montelukast Na together with short-acting beta-agonists. Twenty-four of the patients were using long-acting inhalers with beta-agonists together with inhalers with corticosteroids; 16 of them were also using montelukast Na. Since these asthma drugs have multiple effects on the aortic and peripheral vascular system, we compared the aortic stiffness parameters of these different treatment groups. We did not detect statistically significant differences between the groups ($p > 0.05$).

We evaluated the effects of the presence of atopy and severity of asthma on aortic stiffness parameters. There was no difference in aortic stiffness parameters between atopic asthma patients and the control group (Table 5).

Discussion

The present cross-sectional study was undertaken to comparatively evaluate the elastic properties of the abdominal

Table 1. Characteristics of the asthma patients and control group

	Asthma patients (n = 50)	*Control group (n = 57)*	p-*value*
Gender, female/male	24/26	34/23	> 0.05
Age, years	11.7 ± 2.7	12.3 ± 2.8	> 0.05
Presence of atopy, %	37 (74)	0 (0)	
Immunotherapy	27 (54)	0 (0)	
Duration of diagnosis of asthma, years	8.1 ± 2.8 (3–15)		
Weight, kg	43.0 ± 15.5	47.8 ± 17.0	> 0.05
Height, cm	148.0 ± 15.9	150.4 ± 16.1	> 0.05
BMI, kg/m²	19.0 ± 4.1	20.5 ± 4.3	> 0.05
Systolic blood pressure, mmHg	101.1 ± 10.4	102.4 ± 10.4	> 0.05
Diastolic blood pressure, mmHg	63.5 ± 9.9	64.9 ± 9.8	> 0.05
Mean blood pressure, mmHg	76.0 ± 9.2	77.4 ± 9.3	> 0.05
Heart rate, beat/min	84 ± 15	85 ± 14	> 0.05
Total cholesterol, mg/dl (mmol/l)	152.5 ± 32.6 (3.96 ± 0.84)	147.5 ± 24.6 (3.82 ± 0.64)	> 0.05
LDL cholesterol, mg/dl (mmol/l)	83.6 ± 17.8 (2.17 ± 0.46)	79.6 ± 18.1 (2.06 ± 0.47)	> 0.05
HDL cholesterol, mg/dl (mmol/l)	55.6 ± 17.3 (1.44 ± 0.45)	50.7 ± 11.5 (1.31 ± 0.30)	> 0.05
hs-CRP, mg/dl	2.12 ± 0.41	0.79 ± 0.20	< 0.05
FVC, % predicted	87.3 ± 13.6	87.1 ± 10.6	> 0.05
FEV1, % predicted	97.7 ± 14.9	99.2 ± 11.1	> 0.05
FEV1/FVC, %	95.2 ± 5.8	97.0 ± 4.3	> 0.05
PEF, % predicted	92.8 ± 16.6	89.8 ± 14.6	> 0.05

Data are presented as mean ± standard deviation.
BMI: body mass index, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, HDL: high-density lipoprotein, LDL: low-density lipoprotein, PEF: peak expiratory flow.

Table 2. Echocardiographic findings of the asthma and control groups

	Asthma patients (n = 50)	*Control group (n = 57)*	p-*value*
LVPWTed, mm	7.1 ± 0.1	7.0 ± 0.1	> 0.05
LVED, mm	40.1 ± 4.6	40.4 ± 4.8	> 0.05
LVES, mm	25.8 ± 4.5	24.7 ± 3.9	> 0.05
IVSed, mm	7.4 ± 1.1	7.2 ± 1.1	> 0.05
LA, mm	25.3 ± 4.0	23.2 ± 3.7	> 0.05
Aortic anulus, mm	16.8 ± 3.2	17.1 ± 2.6	> 0.05
EF, %	72 ± 10	76 ± 8	> 0.05
FS, %	36 ± 7	38 ± 7	> 0.05
mPAP, mmHg	19.9 ± 7.1	12.6 ± 6.2	< 0.05

Data are presented as mean ± standard deviation.
EF: ejection fraction, FS: fractional shortening, LA: left atrial diameter, LVED: left ventricular end-diastolic diameter, LVES: left ventricular systolic diameter, LVPWTed: end-diastolic left ventricular posterior wall thickness, mPAP: mean pulmonary artery pressure.

Table 3. Aortic stiffness parameters in the asthma and control groups

	Asthma Patients (n = 50)	*Control Group (n = 57)*	p-*value*
Peak aortic velocity, cm/s	125.6 ± 16.7	123.5 ± 17.9	> 0.05
Ds, mm	11.4 ± 2.0	11.1 ± 1.9	> 0.05
Dd, mm	8.2 ± 1.5	8.2 ± 1.8	> 0.05
DIS, 10^{-6} cm²/dyne	1.35 ± 0.52	1.41 ± 0.66	> 0.05
S	0.38 ± 0.11	0.37 ± 0.14	> 0.05
Ep, N/m²	107.5 ± 39.0	116.5 ± 55.9	> 0.05
Ep*	1.75 ± 0.73	1.83 ± 0.90	> 0.05

Data are presented as mean ± standard deviation.
Dd: abdominal aorta diastolic diameter, DIS: aortic distensibility, Ds: abdominal aorta systolic diameter, Ep: pressure strain elastic modulus, Ep*: pressure strain normalised by diastolic pressure, S: aortic strain.

Table 4. Aortic stiffness parameters in patients with intermediate severity asthma and the control group

	Intermediate-severity asthma patients (n = 18)	*Control group (n = 57)*	p-*value*
Peak aortic velocity, cm/s	125.6 ± 16.7	123.5 ± 17.9	> 0.05
Ds, mm	11.4 ± 2.0	11.1 ± 1.9	> 0.05
Dd, mm	8.2 ± 1.5	8.2 ± 1.8	> 0.05
DIS, 10^{-6} cm²/dyne	1.31 ± 0.51	1.41 ± 0.66	> 0.05
S	0.39 ± 0.10	0.37 ± 0.14	> 0.05
Ep, N/m²	105.9 ± 42.4	116.5 ± 55.9	> 0.05
Ep*	1.71 ± 0.74	1.83 ± 0.90	> 0.05

Data are presented as mean ± standard deviation.
Dd: abdominal aorta diastolic diameter, DIS: aortic distensibility, Ds: abdominal aorta systolic diameter, Ep: pressure strain elastic modulus, Ep*: pressure strain normalised by diastolic pressure, S: aortic strain.

Table 5. Aortic stiffness parameters in asthma patients with atopy and the control group

	Asthma patients with atopy (n = 37)	*Control group (n = 57)*	p-*value*
Peak aortic velocity, cm/s	128.0 ± 16.5	123.5 ± 17.9	> 0.05
Ds, mm	11.5 ± 1.9	11.1 ± 1.9	> 0.05
Dd, mm	8.3 ± 1.3	8.2 ± 1.8	> 0.05
DIS, 10^{-6} cm²/dyne	1.31 ± 0.51	1.41 ± 0.66	> 0.05
S	0.38 ± 0.12	0.37 ± 0.14	> 0.05
Ep, N/m²	105.4 ± 35.6	116.5 ± 55.9	> 0.05
Ep*	1.69 ± 0.66	1.83 ± 0.90	> 0.05

Data are presented as mean ± standard deviation.
Dd: abdominal aorta diastolic diameter, DIS: aortic distensibility, Ds: abdominal aorta systolic diameter, Ep: pressure strain elastic modulus, Ep*: pressure strain normalised by diastolic pressure, S: aortic strain.

aorta in children with asthma and in a control group. Our hypothesis was that since asthma is a chronic inflammatory disease, it could lead to the early development of atherosclerosis in childhood-onset asthma.

To detect the effect of inflammation, we included patients with a diagnosis of asthma of at least three years' duration. As a marker of atherosclerosis, we evaluated abdominal aortic stiffness parameters with transthoracic echocardiography. Stiffness and distensibility assessments of the abdominal aorta play an important role in evaluation of the elasticity of the arterial system. If there is atherosclerosis, aortic stiffness, Ep and Ep* will increase, whereas DIS and S will decrease. S and DIS represent the elasticity of the abdominal aortic wall.

In the literature, aortic distensibility has been shown to be useful in adults as a non-invasive method to detect early atherosclerosis. The increased stiffness causes an increase in pulse pressure and a decrease in diastolic blood pressure, thereby causing increased left ventricular afterload and increased fatigue in arterial wall tissues. Previous studies have shown that measurement of aortic stiffness helps in the early detection of atherosclerosis, and the abdominal aorta becomes stiffer with age, hypertension, atherosclerosis, tobacco-smoking, obesity, and in β-thalassaemia patients and patients with Marfan syndrome and Kawasaki disease.[11,13,14]

Lacombe *et al.* demonstrated that in subjects older than 20 years of age, S, Ep and Ep* were related to age due to atherosclerosis.[10] We calculated S, Ep, Ep* and distensibility using the formula proposed by Lacombe and Lage *et al.*[10,15] Okubo found that aortic distensibility varies with age; it was low in infants, increased gradually to a peak from 10–15 years, and then decreased with age.[11]

Atherosclerosis and asthma are both chronic inflammatory diseases. Inflammation leads to impairment of endothelial function. When the inflammation is chronic, this causes acceleration of atherosclerosis.[18] In the literature, some studies have stated that asthma itself could be a risk factor for heart disase and stroke.[19,20]

Related to increased oxidative stress, asthma is a chronic inflammatory disease.[21] The association between chronic inflammation and oxidative stress is well documented. In asthma patients with inflammatory conditions, elevated levels of reactive oxygen species, such as hydroxyl radicals, superoxides and peroxides have been reported.[22] Chronic inflammation has also been increasingly associated with endothelial dysfunction, atherosclerosis and arterial stiffness, and these in turn with adverse cardiovascular events and common inflammatory pathways.[23,24]

Some studies have evaluated the relationship between adult-onset asthma and atherosclerosis but the results are contradictory. Onufrak *et al.* showed that in adult-onset asthma patients, the risk of atherosclerosis was increased.[25] However, in another study by Otsuki *et al.*, carotid atherosclerosis was reduced in asthmatic adult patients treated with inhaled corticosteroids compared with matched controls, and they found that inhaled corticosteroids had protective effects against atherosclerosis.[26]

Weiler *et al.* found significant correlations between measurements of periferal arterial stiffness and FEV1 in adult asthmatics, and suggested the presence of a common systemic, most likely inflammatory pathway involving both the cardiovascular and respiratory systems.[27] In another study of adult asthmatics, Sun *et al.* found that that patients with severe asthma had increased brachial–ankle pulse-wave velocity (baPWV) compared with those with stable asthma and control subjects. Furthermore, baPWV was elevated in patients with stable asthma compared with the control subjects.[28]

However, there are only a few studies evaluating the relationship between childhood-onset asthma and atherosclerosis. In the study of Cakmak *et al.*,[29] carotid intima–media thickness (CIMT) in asthmatic children was found to be higher compared to the control group and there was a positive correlation between CIMT and total oxidant status. They studied only children with mild asthma who were not using prophylactic inhaled corticosteroids.

In all these studies, CIMT was evaluated as a marker of atherosclerosis. However, in our study, we evaluated abdominal aortic stiffness as a sign of atherosclerosis in childhood asthma.

In our investigation, the study population consisted of children with stable asthma. We did not evaluate aortic stiffness parameters in children with severe asthma. Further studies including larger population size and children with severe asthma may reveal different results regarding abdominal aortic stiffness.

In our study, we used only hs-CRP as an inflammatory marker. An inflammatory marker showing oxidant status could not be studied.

Conclusion

We evaluated aortic stiffness parameters in childhood-onset asthma in children with a diagnosis of asthma of at least three years' duration (average duration from diagnosis: 8.1 ± 2.8 years). We did not find any difference between chidhood-onset asthma patients and the control group with regard to aortic stiffness parameters (DIS, S, Ep and Ep*). There was also no difference in these parameters when we compared patients with mild asthma and those with moderate asthma. These results may be due to the anti-inflammatory effect of inhaled corticosteroid treatment.

Since there is no study in the literature evaluating abdominal aortic stiffness in childhood-onset asthma patients, we could not compare our results with other studies. Further studies are needed to validate these results.

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Is the relationship of body mass index to severity of coronary artery disease different from that of waist-to-hip ratio and severity of coronary artery disease? Paradoxical findings

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Abstract

Background: Although for decades there has been controversy regarding the relationship between obesity and coronary artery disease (CAD), it has been assumed that high body mass index (BMI) is a risk factor for CAD. However, the findings of some recent studies were paradoxical.

Objectives: The aim of this study was to find a relationship between high BMI and waist-to-hip ratio (WHR) with severity of CAD.

Methods: This study was a cross-sectional, prospective study where 414 patients with suspected coronary artery disease, in whom coronary angiography was performed, were enrolled. The mean ± SD of their ages was 61.2 ± 27.4 years (range 25–84), and 250 (60.4%) were male. Regarding cardiovascular risk factors, 113 (27.3%) patients had a history of diabetes mellitus (DM), 162 (39.1%) had hypercholesterolaemia, 238 (57.4%) had hypertension, 109 (26.3%) were current smokers and 24 (5.8%) had a family history of CAD. The mean ± SD of the patients' BMI was 26.04 ± 4.08 kg/m^2 (range 16–39) and means ± SD of their WHR ranged from 0.951 ± 0.07 to 0.987 ± 0.05. The mean ± SD of the severity of CAD according to the SYNTAX and Duke scores were 17.7 ± 9.6 (range 0–64) and 3.2 ± 1.7 (range 0–12), respectively.

Results: In this study, findings showed a negative correlation between the severity of CAD and BMI, according to both SYNTAX and Duke scores ($p \leq 0.001$ and $p = 0.001$, respectively). However, there was a positive correlation between WHR and severity of CAD, according to the Duke score ($p = 0.03$).

Conclusion: BMI had a negative correlation with the severity of CAD, but waist-to-hip ratio had a positive correlation with severity of CAD.

Keywords: body mass index, waist-to-hip ratio, coronary artery disease, SYNTAX score, Duke score

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Although obesity has been regarded as an independent risk factor for coronary artery disease (CAD) by the American Heart Association (AHA) and investigators of the Framingham Heart study in the 1980s and 1990s,[1-3] this has not been supported by recent clinical trials. Moreover, the positive linear relationships between obesity and CAD, as reported by some studies, were as a result of univariate analysis of their data. However, by using multivariate analysis of these study data, which included other cardiovascular risk factors such as diabetes mellitus (DM), hypertension (HTN) and hyperlipidaemia, this relationship was shown to be dramatically reduced.[4,5]

In the Munster Heart study (PROCAM) and similar studies, the positive relationship between body mass index (BMI) and cardiovascular risk factors, with cardiac mortality, which attributed obesity as an independent risk factor, appeared to be due to the associated cardiovascular risk factors that usually accompany obesity.[6-10] In these studies there was also a strong positive correlation between high BMI and other cardiovascular risk factors.

However, findings of recent studies in this regard were opposite to those of previous studies. According to their findings, not only was obesity not a risk factor for CAD but it also had a protective effect on the progression of CAD, which is known as the 'obesity paradox'.[11,12] On the other hand, abdominal adiposity has always been associated with increased cardiovascular disease and mortality rate, independent of patients' weight.[13,14]

This study was designed to evaluate not only the impact of BMI but also waist-to-hip ratio (WHR) on the severity of CAD, based on angiographic findings.

Methods

This study was a cross sectional, prospective study that was conducted in our hospital from September 2009 to March 2011. A total of 414 patients with suspected CAD were enrolled in the study. Patients' mean age ± SD was 61.2 ± 27.4 years (range 24–84) and 250 (60.4%) patients were male.

Coronary angiography was done on all patients. The severity of CAD was measured using the SYNTAX score (the sum of the points assigned to each individual lesion identified in the coronary arteries with > 50% stenosis in vessels > 1.5 mm diameter). The SYNTAX score, a lesion-based angiographic scoring system, was introduced as a tool to grade the complexity of CAD. It was derived from a combination of the AHA classification for coronary artery segments with various other scores,[15,16] and the Duke jeopardy scores (Fig. 1A). The Duke jeopardy score is a simple, effective scoring system for quantifying the amount of myocardium at risk. The Duke jeopardy score, developed by

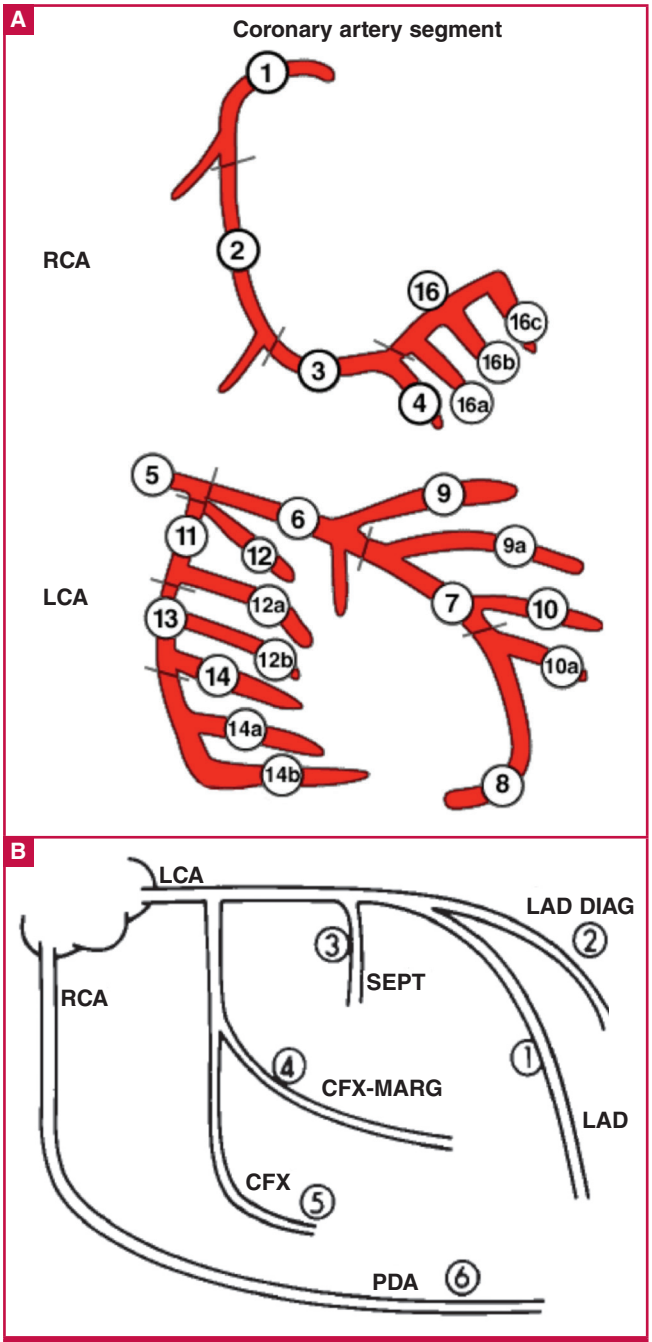

Fig. 1. Diagrams of coronary artery tree demonstrating the 16 segments counted in the SYNTAX score (A), and six segments counted in the Duke jeopardy score (B). CFX = left circumflex coronary artery; CFX-MARG = major marginal branch of the left circumflex coronary artery; LAD = left anterior descending artery; LAD DIAG = major diagonal branch of the left anterior descending artery; LCA = left main coronary artery; PDA = posterior descending coronary artery; RCA = right coronary artery; SEPT = major septal perforating artery. (Adapted from Sianos, *et al. Euro Intervent* 2005; **1**: 219–227, and Califf, *et al. J Am Coll Cardiol* 1985; **5**: 1055.)

Dash *et al.*, 1977,[17] and validated by Califf *et al.*,1985,[18] detects the main vessels affected in their large branches, Fig. 1B).

Coronary angiographies of patients were reviewed by two experts who were blinded to the patients' BMI and WHR. Patients were divided into five groups according to their BMI; normal BMI (21–24 kg/m^2), overweight (25–29 kg/m^2), class I obesity (30–34 kg/m^2), class II obesity (35–39 kg/m^2) and class III obesity (> 40 kg/m^2). Also patients were divided into four groups according to their age; 20–39, 40–59, 60–79 and > 80 years old.

Inclusion criteria were patients over 20 years old who had definite indications for coronary angiography, based on their clinical background. The exclusion criteria were patients unwilling to participate in the study.

For the purpose of multivariate analysis, we included in the study evaluations of conventional cardiovascular risk factors, such as HTN (systolic blood pressure ≥ 140 mmHg and/ diastolic blood pressure ≥ 90 mmHg), DM [fasting blood sugar > 126 mg/dl (6.99 mmol/l) and/glycosylated haemoglobin (HbA_{1c}) > 6%], hyperlipidaemia [low-density lipoprotein (LDL) cholesterol > 120 mg/dl (3.11 mmol/l) and triglycerides > 150 mg/dl (1.7 mmol/l)], family history of CAD and cigarette smoking (current smoker: at least five cigarettes/day for ≥ one year).

Statistical analysis

For analysing data, SPSS version 15 (USA, Illinois, Chicago) was used. The Student's *t*-test was used for comparing quantitative variables between two groups and the one-way ANOVA test was used for comparing means of quantitative variables between groups. Logistic regression was used for multivariate analysis of compounding factors. Chi-square and Fisher's exact tests were used for analysis of qualitative variables and a *p*-value ≥ 0.05 was considered significant.

Results

Of 414 (100%) patients, 250 (60.4%) were male and their ages ranged from 25 to 84 years. The prevalences of DM, HTN, hyperlipidaemia, family history of CAD and cigarette smoking were 27.3, 29.5, 39.1, 5.8 and 26.3%, respectively. Basic clinical and demographic characteristics of the patients are presented in Table 1.

The severity of CAD was measured by the SYNTAX and Duke jeopardy scores. For the SYNTAX score, the mean ± SD of the patients' scores was 17.7 ± 9.6 (range 0–64) and for the Duke score, it was 3.2 ± 1.7 (range 0–12). There was a negative correlation between the SYNTAX and Duke scores (severity of CAD) and the patients' BMI ($p = 0.01$ and $p = 0.001$, respectively).The correlation between the patients' BMI and the severity of CAD (SYNTAX and Duke scores) is presented in Table 2.

There was an inverse relationship between obesity and the severity of CAD, according to the SYNTAX and Duke criteria, which has been defined as the 'obesity paradox'. In order to rule out the impact of other cardiovascular risk factors, multivariate regression analysis was performed. Regression analysis revealed a β-coefficient of –0.14 for the Duke score and –0.17 for the SYNTAX score. This means that for every unit increase in BMI there would be a 0.14 and 0.17 decrease in the severity of CAD according to the Duke and SYNTAX scores, respectively. After adjusting for confounding factors, there was still a significantly negative correlation between BMI and severity of CAD (p = 0.028 and 0.01, respectively). Meanwhile multivariate analysis

Table 1. Basic clinical and demographic characteristics of patients.

Characteristics	*Number (%)*
Age, mean ± SD (years)	61.2 ± 27.4
Male gender	250 (60.4)
Diabetes mellitus	113 (27.3)
Hypertension	122 (29.5)
Hyperlipidaemia	162 (39.1)
History of CAD	24 (5.8)
Cigarette smoking	109 (26.3)
History of AP	254 (85.5)
History of MI	85 (20.5)

CAD = coronary artery disease, AP = angina pectoris, MI = myocardial infarction.

revealed a positive correlation between severity of CAD and cardiovascular risk factors (Table 3).

On the other hand, our findings regarding the relationship between WHR and severity of CAD, based on the Duke myocardial jeopardy score, showed a positive correlation between the two variables (p = 0.03). With increasing WHR, the Duke score also increased. The relationship between severity of CAD (Duke score) and WHR is presented in Table 4.

Discussion

In this study, there was a paradoxical relationship between BMI and severity of CAD but not between WHR and severity of CAD. Based on the SYNTAX and Duke scores, β-coefficients between BMI and severity of CAD before multivariate analysis were –0.2 and –0.18, respectively. After multivariate analysis, they were –0.17.and –0.14, respectively. This shows an inverse relationship between BMI and severity of CAD.

Controversy regarding the correlation between obesity and CAD, which surfaced a few decades ago, was the motivation for us to conduct this study. Although it seems logical that obesity or adiposity should be accompanied by more accumulation of fat cells everywhere in the body, including vascular walls (atherosclerotic plaques), it must be clarified that first of all, obesity *per se* is not adiposopathy, and second, the process of atherosclerosis is not a simple process of fat accumulation.[19,20]

The process of atherosclerosis is inflammation as a result of the response to injury in the milieu of high intravascular LDL cholesterol, especially oxidised LDL. It seems that visceral adipose tissue is metabolically more active and pathological than subcutaneous adipose tissue, and induces immunity processes that contribute to atherosclerotic cardiovascular disease.[21-24] The

Table 2. Correlation between BMI and severity of CAD (SYNTAX and Duke scores)

BMI (kg/m²)	*Number of patients (%)*	*SYNTAX score (mean ± SD)*	*Duke score (mean ± SD)*
20–24	169 (40.8)	22.3 ± 17.2	4.01 ± 3.3
25–29	154 (37.2)	16.1 ± 14.6	3.05 ± 2.5
30–34	83 (20.1)	12.1 ± 9.2	2.3 ± 1.1
35–39	8 (1.9)	10.8 ± 7.04	1.8 ± 1.04
p-value	–	0.01	0.001

BMI = body mass index

Table 3. Correlation between cardiovascular risk factors and severity of CAD (Duke and SYNTAX scores)

Risk factors	*Duke score (mean ± SD)*	p-*value*	*SYNTAX score (mean ± SD)*	p-*value*
Hypertensives	3.6 ± 1.7	0.04	19.1 ± 13.1	0.03
Normotensives	2.4 ± 1.9		14.9 ± 9.5	
Cigarette smokers	3.8 ± 1.2	0.02	20.8 ± 17.4	0.03
Non-smokers	3.07 ± 1.4		16.6 ± 14.2	
Hyperlipidaemics	3.9 ± 1.5	0.001	31.5 ± 18.05	0.001
Normolipidaemics	2.8 ± 1.2		15.3 ± 11.02	
Diabetics	4.1 ± 3.6	0.002	21.5 ± 18.4	0.008
Non-diabetics	2.9 ± 1.3		16.3 ± 9.2	
FH positive	4.5 ± 3.1	0.07	21.9 ± 14.2	0.3
FH negative	3.1 ± 2.3		17.5 ± 10.4	

FH = family history.

answer to the question raised from the obesity paradox is that atherosclerotic disease does not result from the accumulation of adipose tissue *per se* but is as a result of adipose tissue dysfunction, or 'sick fat'.[19,23,24]

Rubinshtein and colleagues (2006), in their study on 928 patients with CAD, showed that obesity had an inverse relationship with the severity of CAD but other risk factors such as DM, hyperlipidaemia and male gender were correlated with the severity of CAD.[11] In another study, published in 2007 by Niraj and colleagues, which was similar to our study, the relationship between severity of CAD and BMI according to the Duke score was also paradoxical.[10] Although there are similarities between our study and theirs regarding the inverse relationship between patients' BMI and the severity of CAD, in our study the relationship between WHR and severity of CAD was evaluated simultaneously. Surprisingly, in our study, WHR was correlated with the severity of CAD based on the Duke score.

Moreover, according to the studies of Morricone, Empana and Zhang, which were published in 1999, 2004 and 2008, respectively, abdominal adiposity and severity of CAD were correlated.[12-14] Although their findings were similar to ours regarding correlation between WHR/abdominal obesity and severity of CAD, they did not compare BMI with WHR regarding their impact on the severity of CAD, as we did. These studies showed that, first, high BMI *per se* was not a risk factor for CAD, and second, high WHR/abdominal obesity was a risk factor for CAD. That means abdominal fat accumulation is more pathological (adiposopathic) than subcutaneous fat ccumulation.[19,24]

Table 4. Relation between WHR and severity of CAD based on the Duke score

WHR (mean ± SD)	*Number of patients*	*Duke score*
0.951 ± 0.07	165	0
0.954 ± 0.06	62	2
0.957 ± 0.07	58	4
0.962 ± 0.05	54	6
0.971 ± 0.05	44	8
0.979 ± 0.02	24	10
0.987 ± 0.05	6	12
p-value	0.03	

WHR = waist-to-hip ratio.

Although in our study, regression analysis for confounding factors such as DM, HTN, cigarette smoking and hyperlipidaemia revealed a statistically significant correlation between them and the severity of CAD ($p = 0.002$, $p = 0.001$, $p = 0.04$ and $p = 0.02$, respectively), after omission of confounding factors, there was still a paradoxical relationship between BMI and severity of CAD. β-coefficients before multivariate analysis were –0.2 and –0.18, and after multivariate analysis they were –0.17 and –0.14, based on the SYNTAX and Duke scores, respectively. This showed an inverse relationship between BMI and severity of CAD.

The limitation of our study was that lower BMI (20–24 kg/m^2) was more prevalent (56.2%) in the older age groups (> 60 years), and higher BMI (30–34 kg/m^2) was more common (57.8%) in the younger age groups (40–59 years). As in the study by Niraj *et al*.,[11] it can be concluded that patents with a higher BMI have been evaluated earlier for CAD. This indicates a need for a larger study with more age-matched groups.

Conclusion

The findings of this study, paradoxically, showed a negative correlation between BMI and the severity of CAD, but a positive correlation between WHR and the severity of CAD.

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Effect of hypothermia in patients undergoing simultaneous carotid endarterectomy and coronary artery bypass graft surgery

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Abstract

Purpose: We sought to determine whether hypothermia provided any benefit in patients undergoing simultaneous coronary artery bypass graft surgery (CABG) and carotid endarterectomy (CEA) using one of two different surgical strategies.

Methods: Group 1 patients (n = 34, 88.2% male, mean age 65.94 ± 6.67 years) underwent CEA under moderate hypothermia before cross clamping the aorta, whereas group 2 patients (n = 23, 69.6% male, mean age 65.78 ± 9.29 years) underwent CEA under normothermic conditions before initiating cardiopulmonary bypass (CPB). Primary outcome of interest was the occurrence of any new neurological event.

Results: The two groups were similar in terms of baseline characteristics. Permanent impairment occurred in one patient (2.9%) in group 1. One patient from each group (2.9 and 4.3%) had transient neurological events and they recovered completely on the sixth and 11th postoperative days, respectively. Overall, there was no statistically significant difference between the two groups with regard to occurrence of early neurological outcomes (n = 2, 5.8% vs n = 1, 4.3%, p = 0.12).

Conclusions: This study could not provide evidence regarding benefit of hypothermia in simultaneous operations for carotid and coronary artery disease because of the low occurrence rate of adverse outcomes. The single-stage operation is safe and completion of the CEA before CPB may be considered when short duration of CPB is required.

Keywords: carotid endarterectomy, coronary artery disease, hypothermia

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The co-existence of coronary, carotid, peripheral and renal atherosclerotic diseases is not infrequent and it was reported that 24% of patients with coronary artery disease have at least one additional atherosclerotic lesion.[1] In previous studies, 4.6 to 8.0% of patients with coronary artery disease (CAD) had severe coronary artery stenosis (CAS), the extent of the atherosclerotic involvement being significantly correlated with the carotid and coronary arteries.[2,3] Simultaneous surgical management of concomitant coronary and carotid artery disease has been the focus of interest in the past two decades since success rates of coronary artery bypass grafting (CABG) has substantially increased while a preventive approach for adverse neurological outcomes has gained popularity.[4] Carotid stenosis and previous history of cerebrovascular disease were reported to be among the most prominent risk factors for peri-operative stroke and neurocognitive decline in patients undergoing CABG.[5]

The optimal decision for the timing of carotid endarterectomy (CEA) is controversial in patients submitted for CABG since data focusing on establishing the best strategy of practice are limited.[6] There have been numerous cross-sectional studies reporting favourable outcomes for both simultaneous and staged CEA and CABG procedures,[7-9] and some authors have suggested that the decision to perform the two procedures simultaneously should be made based on strict patient selection criteria.[10] Nevertheless, delaying the CEA was found to be an independent predictor of early stroke and death in one recent randomised trial.[11] This uncertainty led to an increasing trend towards individualisation of the treatment in patients with concomitant disease.

Some earlier studies implied the potential role of hypothermia as a preventative measure against adverse postoperative outcomes in patients undergoing single-stage on-pump CABG and CEA.[12,13] However, these studies fell short of their goal of determining whether hypothermia provides protection, because none of them involved a control group of patients undergoing CEA under normothermic conditions. In this study we sought to determine whether hypothermia provided any benefit in patients undergoing simultaneous CABG and CEA using one of two different surgical strategies.

Methods

This retrospective cohort study was undertaken in a single tertiary educational hospital and was made up of 57 patients who underwent concomitant CEA and CABG between 2006 and 2013. Patients' archived records, counselling charts and laboratory tests were reviewed in January 2013.

Patients were divided into two groups. Group 1 patients (n = 34, 88.2% male, mean age 65.94 ± 6.67 years) were those undergoing CEA under moderate hypothermia, after initiation of cardiopulmonary bypass (CPB) and before cross clamping

the aorta, whereas group 2 patients (n = 23, 69.6% male, mean age 65.78 ± 9.29 years) were those undergoing CEA under normothermic conditions before initiation of CPB.

According to our institution's policy, patients scheduled for CABG undergo duplex ultrasound scans for screening of CAS, and those with ≥ 70% stenosis and/or plaque ulceration in at least one carotid artery undergo carotid angiography. It was the surgeon's discretion which procedure would be performed in any given patient during the study period, but this decision was not made on characteristics or certain risk factors that the patient had.

Patients undergoing emergency operation, multiple interventions including valve, ascending aorta and left atrial size reduction were excluded. Patients with a history of recent cerebral infarction, transient or permanent ischaemic stroke and/or cerebral bleeding were also excluded.

Daily neurological assessment by physicians of patients undergoing CEA has been the standard of care in this institution. Daily chart notes were carefully inspected for records regarding neurological status of the patients. Based on these observations, the primary outcome of interest was considered occurrence of any new neurological event, including seizures, coma and/or ipsilateral or contralateral motor or sensorial involvement during the postoperative period. Beginning on the day after the operation, all patients were given subcutaneous low molecular weight heparin and aspirin until discharge home.

All operations were performed under general anaesthesia. In both groups, common, internal and external carotid arteries were exposed first through a standard approach anterior to the sternocleidomastoid muscle. In group 1, a median sternotomy was made, the internal thoracic artery was harvested, 350 UI/kg of systemic heparin was administered and cardiopulmonary bypass was established in a standardised fashion.

The carotid arteries were clamped when the systemic temperature had cooled down to moderate hypothermia. CEA was performed, clamps were removed and the neck incision was left open until heparin reversal by applying sponges over the wound. The surgeon then cross clamped the aorta and proceeded with the CABG procedure in a standardised fashion.

In group 2, systemic heparin was administered in similar doses and CEA was performed before the sternotomy was made. The clamps were removed and the neck incision was left open by applying sponges. The surgeon proceeded with a median sternotomy and the standardised CABG procedure thereafter.

In both groups, the arteriotomy was closed primarily in all patients without using intraluminal shunts. Cardiac arrest was established by antegrade normothermic blood cardioplegia and proximal anastomoses were performed with an aortic side-biting clamp.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 packaged software. Normal distribution of variables was tested using visual histograms and the Kolmogorov–Smirnov test. Descriptive statistics for continuous variables were reported as mean ± SD and descriptive statistics for categorical variables were reported as frequency and percentage. Categorical variables were compared using the chi-square or Fisher's exact tests, where appropriate. Continuous variables were compared using the independent samples t-test. Since new neurological events occurred in very few patients, no additional tests (univariate or multivariate analysis) were performed to identify independent predictors of adverse outcomes. Study power was tested using G-power software.

Results

Baseline patient characteristics were similar between the two groups (Table 1). The mean time of CPB was shorter and mean level of hypothermia was lower in group 1 patients than in those in group 2. There was no difference between the two groups regarding other operative values (Table 2). A total of 28 patients (82.3%) in group 1 and 18 patients (78.2%) in group 2 were asymptomatic for neurological complaints (p = 0.76).

Overall, early mortality occurred in one patient from each group (n = 2, 3.7%, p = 0.86). Both patients died of low cardiac output syndrome. Adverse neurological outcome with permanent impairment occurred in one patient (2.9%) from group 1. One patient from each group (2.9 and 4.3%) had transient neurological events but they recovered completely on the sixth and 11th postoperative days, respectively.

Table 1. Baseline characteristics

Variables	*Group 1* n *(%)*	*Group 2* n *(%)*	p
Men	30 (88.2)	16 (69.6)	0.09
Age	65.94 ± 6.67	65.78 ± 9.29	0.9
Previous MI	9 (26.5)	6 (26.0)	0.97
Unstable angina	3 (8.8)	1 (4.3)	0.64
Previous CVA	11 (32.3)	5 (21.7)	0.48
Stroke	4 (11.8)	1 (4.3)	0.63
Hypertension	29 (85.3)	18 (78.3)	0.50
Diabetes	17 (50)	12 (52.2)	0.87
Hyperlipidaemia	19 (55.9)	9 (39.1)	0.21
Renal failure	4 (11.8)	1 (4.3)	0.63
Smoking	27 (79.4)	14 (60.9)	0.12
PAD	13 (38.2)	7 (30.4)	0.54

MI; myocardial infarction, CVA: cerebrovascular accident, PAD; peripheral arterial disease.

Table 2. Operative variables

Variables	*Group 1* n *(%)*	*Group 2* n *(%)*	p
Number of bypass grafts	2.9 ± 0.6	2.9 ± 0.8	0.91
CPB time (min)	72.3 ± 21.9	59.6 ± 20.8	0.03
Time of cross clamping (min)	32.6 ± 9.4	31.2 ± 6.9	0.78
Carotid clamping time (min)	9.8 ± 2.7	9.7 ± 3.1	0.91
Hypothermia	30.3 ± 1.3	35.8 ± 0.7	0.001
Left CEA, *n* (%)	17 (50)	14 (61)	0.41

CPB; cardiopulmonary bypass, CEA; carotid endarterectomy.

Table 3. Postoperative variables

Variables	*Group 1* n *(%)*	*Group 2* n *(%)*	p
Early neurological outcomes	2 (5.8)	1 (4.3)	0.12
Intensive care unit stay (day)	2.9 ± 1.7 (1–9)	3.1 ± 2.2 (1–11)	0.21
Hospital stay (day)	5.2 ± 4.5 (4–8)	5.3 ± 4.2 (4–9)	0.19

Overall, there was no significant difference between the two groups with regard to occurrence of early neurological outcomes ($n = 2$, 5.8% vs $n = 1$, 4.3%, $p = 0.12$) (Table 3). None of the patients had revision for bleeding, cardiac tamponade, low cardiac output syndrome, arrhythmia and systemic, respiratory or wound infection. The length of intensive care unit stay and hospital stay were similar between the two groups (Table 3).

Because of the limited sample size (34 vs 23 patients) and very low occurrence rate of neurological events, the study power (1-β error) was quite low (< 25%) in this study to provide evidence for rejection of the null hypothesis. When significantly shorter mean CPB time in group 2 than in group 1 patients (59.6 ± 20.8 vs 72.3 ± 21.9) was considered as a secondary outcome, our study had 71% power (1-β error) with an α error of 0.05 and an estimated effect size of 0.60 (medium effect size).

Discussion

Our study showed that single-stage CEA and CABG is safe and carotid intervention may be performed either before or after initiation of CPB without adding much more complexity to the procedure. However, because of the low effect size, which is a direct measure of the occurrence rate of the outcomes, our study could not draw a definitive conclusion regarding the protective effect of hypothermia during CEA.

The decision whether each patient would receive CEA under hypothermia or not was the surgeon's discretion in general, and this decision was not dependent on objective criteria. However, it could not be totally neglected that the surgeon might preferentially have intended to take the short CPB time into consideration and performed CEA initially in the presence of certain conditions or features, such as patient fragility or poor coronary arterial structure. These features were not taken into consideration as potential risk factors since patient records were not standardised to provide objective information.

In addition, the majority of our patients were asymptomatic of neurological complaints, which was another known risk factor for the development of neurological events after simultaneous CEA and CABG surgery. The operations were performed within a period of seven years, in which the standard of surgical approach did not undergo modification by the surgeon.

Similar to ours, in one earlier study where Di Tommaso *et al*.[12] performed 73 combined CEA and CABG procedures, the occurrence rate of temporary neurological deficits was quite low (five patients), and an additional six patients had cerebrovascular events during the late follow up. These authors attributed the low rate of neurological complications to CPB-related benefits, including haemodilution, pulsatile flow and hypothermia.

Yildirim *et al*.[14] used a similar technique for single-stage operation and reported that four of 72 patients had neurological complications and two of these became permanently disabled. In a report on a small series of patients, neurological events occurred in one of 15 patients undergoing combined CEA and CABG under mild hypothermia.[15] Finally, Sadeghi *et al*.[13] reported no early neurological outcomes and only one stroke during follow up when CEA was performed under mild hypothermia.

Although all these studies have implied that hypothermia is likely to have cerebral protective effects, our results and those of others suggest that the lower complication rates may not only be produced by the effect of hypothermia but may also be related to the surgeons' cumulative experience with the CEA technique.

Darling *et al*.[16] reported in their series of 420 patients that the risk of stroke was 1.2% and mortality was 2.4% in patients undergoing CEA prior to CABG. Another study showed that rate of major stroke was 3.3%, whereas transient neurological deficit rate was 9.9%[17] in 30 patients undergoing CEA before CABG. Santos *et al*.[7] recommended a < 30-day peri-operative period between initial CEA and CABG. Although some authors[10] have suggested that the indication for performing combined CEA and CABG should be restricted to patients requiring urgent CABG, we believe that a single-stage operation would often be the desired option both for the surgeon and the patient, provided that there would be no additional risks using a combined technique.

We are aware that our study had many limitations, including retrospective design, lack of randomisation, single institution experience and small sample size. Also, patients in this study were not divided into treatment arms based on objective criteria, a fact that may be a source of potential bias. Finally, follow-up information was not sufficient to report since the majority of patients could not respond to our invitation for follow up because they lived in distant regions of the country.

Conclusions

Low rate of adverse neurological outcomes after simultaneous CABG and CEA under CPB were previously attributed to hypothermia by a possible mechanism of reducing neuronal ischaemia. However, our study and previous ones showed that it is difficult to establish such a relationship due to low occurrence of adverse outcomes after combined operations. Single-stage operation is effective and safe, and performing the CEA before initiation of CPB may be considered when short duration of CPB is required.

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Losing weight at any age can improve cardiovascular health

Weight loss at any age in adulthood is worthwhile because it could yield long-term heart and vascular benefits. The results are from a study ongoing from 1946, examining the impact of lifelong patterns of weight change on cardiovascular risk factors in a group of British men and women followed since birth.

They showed that the longer the exposure to excess body fat (adiposity) in adulthood, the greater the cardiovascular-related problems in later life, including increased thickness of the carotid artery walls, raised systolic blood pressure, and increased risk of diabetes. The findings were published online on 21 May 2014 in the *Lancet Diabetes & Endocrinology.*

For the first time, the findings also indicate that adults who drop a body mass index (BMI) category, from obese to overweight, or from overweight to normal at any time during adult life, even if they regain weight, can reduce these cardiovascular manifestations.

The study used data from 1 273 men and women from the UK Medical Research Council National Survey of Health and Development (NSHD). Participants were classified as normal weight, overweight or obese in childhood and at 36, 43, 53 and 60–64 years of age. Cardiovascular phenotyping between the ages of 60 and 64 years with carotid intima–media thickness (cIMT; a surrogate marker for cardiovascular events) was used to assess the effect of lifetime exposure to adiposity on cardiovascular risk factors.

Prof John Deanfield, lead author, from University College London (UCL) said, 'Our study is unique because it followed individuals for such a long time, more than 60 years, and allowed us to assess the effect of modest, real-life changes in adiposity. Our findings suggest that losing weight at any age can result in long-term cardiovascular health benefits, and support public health strategies and lifestyle modifications that help individuals who are overweight or obese to lose weight at all ages.'

Elizabeth Cespedes and Frank Hu from the Harvard School of Public Health, Boston, USA, commented on the study. 'Although it is encouraging that even transitory weight loss during adulthood has cardiovascular benefits, only 2% of participants in the present study had a sustained reduction in BMI category in adulthood, underscoring the importance of weight maintenance and prevention of weight gain as priorities for public health programming and policy. Improvements in diet and increases in physical activity are crucial levers of long-term weight maintenance and prevention of weight gain in middle-age and early adulthood.

Overweight individuals might have even greater health benefit from lifestyle changes such as increased physical activity than do normal-weight individuals. The results of this study affirm a continued emphasis on public health policies that enable lifestyle changes to achieve and, especially, to maintain a healthy BMI.'

They add, 'Ideally, future research will address long-term patterns of intentional versus unintentional weight loss, the means to achieve weight loss and the weight loss maintenance necessary to reduce cardiovascular endpoints.'

Source

http://www.diabetesincontrol.com/articles/53-/16395-losing-weight-at-any-age-can-improve-cardiovascular-health.

Circulating adhesion molecules and arterial stiffness

Ismail Dogu Kilic, Gulin Findikoglu, Yusuf I Alihanoglu, Bekir Serhat Yildiz, Sukriye Uslu, Simin Rota, Harun Evrengul

Abstract

Aim: VCAM-1 and ICAM-1 are two important members of the immunoglobulin gene superfamily of adhesion molecules, and their potential role as biomarkers of diagnosis, severity and prognosis of cardiovascular disease has been investigated in a number of clinical studies. The aim of the present study was to determine the relationship between circulating ICAM-1 and VCAM-1 levels and aortic stiffness in patients referred for echocardiographic examination.

Methods: Aortic distensibility was determined by echocardiography using systolic and diastolic aortic diameters in 63 consecutive patients referred for echocardiography. Venous samples were collected in the morning after a 12-hour overnight fast, and serum concentrations of ICAM-1 and VCAM-1 were measured using commercial enzyme immunoassay kits.

Results: Data of a total of 63 participants (mean age 55.6 ± 10.5 years, 31 male) were included in the study. Circulating levels of adhesion molecules were VCAM-1: 12.604 ± 3.904 ng/ml and ICAM-1: 45.417 ± 31.429 ng/ml. We were unable to demonstrate any correlation between indices of aortic stiffness and VCAM-1 and ICAM-1 levels.

Conclusion: The role of soluble adhesion molecules in cardiovascular disease has not been fully established and clinical studies show inconsistent results. Our results indicate that levels of circulating adhesion molecules cannot be used as markers of aortic stiffness in patients.

Keywords: VCAM-1, ICAM-1, adhesion molecules, aortic stiffness

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Damage to or stimulation of the endothelium leads to the increased expression and release of molecules that trigger leukocyte homing, adhesion and migration into the subendothelial space, which are fundamental stages of the development and progression of atherosclerosis.[1] Among these, adhesion molecules play a key role. Adhesion molecules are substances that mediate the interaction between cells, their extracellular matrices and endothelial surfaces. They function as receptors that trigger intracellular pathways and participate in the control of vital processes.[2]

Once expressed on the endothelial surface, soluble forms of adhesion molecules may be found in the circulation, released either via shedding or proteolytic cleavage, and are considered markers of increased expression of membrane-bound adhesion molecules.[3-5] Vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) are two important members of the immunoglobulin gene superfamily of adhesion molecules and their potential role as biomarkers of diagnosis, severity and prognosis of cardiovascular disease has been investigated in a number of clinical studies.[6]

Decreased arterial compliance is one of the earliest signs of adverse structural and functional changes within the vessel wall.[7] Increased arterial stiffness represents a physiological aspect of ageing, however, this process can be accelerated by cardiovascular risk factors, and has been shown to be an independent predictor of cardiovascular morbidity and all-cause mortality in various populations.[8-10]

Although studies have also demonstrated that increased arterial stiffness is associated with inflammation, data on the association between aortic distensibility and soluble adhesion molecules are sparse.[11] The purpose of the present study was to determine the relationship between circulating ICAM-1 and VCAM-1 levels as inflammatory markers, and aortic stiffness in patients referred for echocardiographic examination.

Methods

Sixty-three consecutive patients who were referred for echocardiography were included in the study. Patients with renal or hepatic failure, known infectious or inflammatory disease, acute illness, moderate-to-severe valvular dysfunction, aortic dissection or other aortic disease, or poor acoustic quality were excluded. The study was approved by our local ethics committee, and written informed consent was obtained from each participant.

Aortic stiffness measurements were performed on the subjects in the left lateral decubitus position with echocardiography, using a Vivid 7 Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway) with a 2.5-MHz probe. The aortic diameter was recorded by M-mode echocardiography at a level of 3 cm above the aortic valve.

Internal aortic diameters were measured by means of a caliper in systole and diastole as the distance between the trailing edge of the anterior aortic wall and the leading edge of the posterior

Table 1. Baseline characteristics of the patients

Characteristics	*Number (%)*
Age (years)	55.6 ± 10.5
Males	31 (49.2)
Smoking	6 (9.5)
Hypertension	31 (49.2)
Diabetes mellitus	14 (22.2)
Hyperlipidaemia	11(17.5)
Coronary artery disease	18 (25.6)

aortic wall. Aortic systolic (AoS) diameter was measured at the time of full opening of the aortic valve, and diastolic (AoD) diameter was measured at the peak of QRS. Three consecutive beats were measured routinely and averaged.

Systolic and diastolic blood pressures were measured simultaneously at the brachial artery by sphygmomanometry. Pulse pressure was calculated as systolic minus diastolic blood pressure.

The percentage change of the aortic root Ao (%) was calculated to obtain the aortic strain:

$$\text{Ao (\%)} = \frac{100 \times (\text{AoS} - \text{AoD})}{\text{AoD}}$$

Other indices of the aortic elastic properties were measured.

Aortic distensibility index (cm^{-2} dyn^{-1} 10^{-6})

$$= \frac{2 \times (\text{systolic diameter} - \text{diastolic diameter})}{(\text{diastolic diameter}) \times (\text{pulse pressure})}$$

$$\text{The aortic stiffness index } \beta = \frac{\ln(\text{SBP/DBP})}{(\text{AoS}-\text{AoD})/\text{AoD}}$$

All venous samples were collected in the morning after a 12-hour overnight fast, for biochemical analyses. The blood samples were centrifuged at 4 000 rpm at room temperature for 5 min, and the plasma was frozen at –20°C until measurement of adhesion molecules. Serum concentrations of ICAM-1, and VCAM-1 were measured using commercial enzyme immunoassay kits (E-BIOSCIENCE, San Diego, USA), as instructed by the manufacturer.

Statistical analysis

All data analyses were performed with the SPSS (Statistical Package for Social Sciences) for Windows 17.0 computer program (SPSS Inc. Chicago, IL, USA). Data were expressed as mean ± standard deviation. After testing for normality with the Shapiro–Wilk test, continuous parameters were analysed with non-parametric tests. The relationship between levels of circulating adhesion molecules and aortic stiffness was assessed by Spearman's test. Since preliminary analysis did not reveal significant interactions with cellular adhesion molecules, we did not run models stratified by risk factors for aortic stiffness. A p-value of < 0.05 was accepted as significant.

Results

Data from a total of 63 participants (mean age 55.6 ± 10.58 years, 31 male) were included in the study. The baseline characteristics of the study population are summarised in Table 1. Circulating levels of adhesion molecules were VCAM-1: 12.604 ± 3.904 ng/ml and ICAM-1: 45.417 ± 31.429 ng/ml. Aortic strain was 6.210 ± 2.253%, stiffness index was calculated as 10.423 ± 5.350 and distensibility as 2.354 ± 0.993 × 10^{-3} /KPa (Table 2). We were unable to demonstrate any correlation between the indices of aortic stiffness and CAM-1 and ICAM-1 levels (Table 3).

Table 2. Serum VCAM and ICAM levels and indices of aortic stiffness

Variables	*Mean ± SD (n = 63)*
VCAM (ng/ml)	12.604 ± 3.904
ICAM (ng/ml)	45.417 ± 31.429
Aortic strain (%)	6.210 ± 2.253
Stiffness index (β)	10.423 ± 5.350
Distensibility (× 10^{-3}/KPa)	2.354 ± 0.993

Discussion

The potential role of soluble adhesion molecules as biomarkers of diagnosis, severity and prognosis of cardiovascular disease have been investigated in a number of clinical studies. However, these studies have found heterogeneous results. Ridker *et al.* reported a significant association between increasing concentrations of sICAM-1 and the risk of future myocardial infarction, especially among participants with baseline sICAM-1 concentrations in the highest quartile.[12]

Blankenberg *et al.* found that VCAM-1, ICAM-1 and E-selectin were significantly related to future cardiovascular death in 2.7 years' mean follow up of a prospective cohort of 1 245 patients.[3] Moreover, of all the inflammatory markers evaluated, VCAM-1 levels revealed the strongest association with future death, and added predictive value to the classic risk factors and high-sensitivity C-reactive protein (CRP) in determining the risk for future cardiovascular death.

In a prospective, nested, case–control study, median levels of sICAM-1 but not sVCAM-1 were significantly higher at baseline among men who developed peripheral arterial disease (PAD) during a nine-year follow-up period.[13] In the study by Hwang *et al.*, E-selectin and ICAM-1 levels were significantly increased in patients with coronary heart disease (CHD) and carotid artery atherosclerosis compared with the control subjects. However, levels of VCAM-1 were not significantly different among patients in these groups.[14]

In contrast to these findings, in a long-term, community-based study, Malik *et al.* assessed the predictive ability of baseline serum concentrations of soluble adhesion molecules for fatal and non-fatal CHD. They found no strong association of these adhesion molecules with CHD risk. Furthermore, they reinforced their findings with a meta-analysis of previously published prospective studies.[15]

Table 3. Correlation between aortic strain, stiffness index, distensibility and adhesion molecules

Variables	*VCAM (ng/ml)*		*ICAM (ng/ml)*	
	r	*p*	*r*	*p*
Aortic strain (%)	–0.030	0.813	0.061	0.634
Stiffness index (β)	0.038	0.768	–0.095	0.458
Distensibility (× 10^{-3}/KPa)	–0.026	0.839	0.097	0.449

Whether soluble adhesion molecules are increased in subclinical cardiovascular disease has been investigated in several studies. In a sample from the Monitoring Trends in and Determinants in Cardiovascular Disease (MONICA) trial, despite sICAM-1 levels being independently associated with the risk of having at least one carotid or femoral plaque, no significant association was found with carotid intima–media thickness (CIMT).[16] Similarly, Amar *et al*. showed interleukin-6 and ICAM levels were associated with stable atherosclerotic plaque but not with IMT.[17]

In a prospective study by Gross *et al*., higher sICAM1 levels were associated significantly and in a graded fashion with common CIMT in participants with advanced plaque.[18] The study indicated an early (mean age 40 years) involvement of sCAM1 in the development of atherosclerosis, independent of traditional cardiovascular risk factors and CRP levels. Moreover, no association was found in patients with low total burden of atherosclerosis.

Our results are in alignment with these studies. In consecutive patients referred for echocardiographic examination, we found no association between adhesion molecules and aortic stiffness, which is a predictor of cardiovascular disease.

Despite all these studies, the role of soluble adhesion molecules in cardiovascular disease has not been fully established and clinical studies show inconsistent results. There are some possible explanations for this inconsistency. First, vascular endothelial and smooth muscle cells express VCAM-1, while ICAM-1 expression is not limited to these cells and is expressed in many cells, including haematopoietic cells and fibroblasts.[3] Therefore, VCAM-1 may be a marker of plaque burden or activity, whereas ICAM-1 may be a marker of low-grade inflammation. Some authors have suggested that ICAM-1 is predictive in initially healthy people and VCAM-1 in patients with atherosclerosis.[3]

Second, levels of soluble adhesion molecules are influenced by age, smoking status, diabetes and other inflammatory conditions, and even with exercise or changes in arterial pressure.[19,20] Moreover, there is a lack of knowledge of which cellular and molecular factors determine the levels of adhesion molecules, since VCAM and ICAM, like other inflammatory molecules, may have regulations at many levels.[6]

Aortic stiffness is an independent predictor of cardiovascular risk. Arterial stiffening is a physiological aspect of ageing and is the result of the joint effects of adhesion molecules, integrins, metalloproteinases, the renin–angiotension system, and inflammation of cellular components (endothelium, vascular smooth muscle, fibroblasts and matrix components) on the structural and functional properties of the artery.[21] Indeed, recent studies have shown the importance of inflammation in arterial stiffening. Increased levels of inflammatory markers have been associated with arterial stiffness in various groups, including healthy subjects, hypertensives, and community-based groups.[21-25]

In the study of Bussel *et al*., biomarkers of endothelial dysfunction and low-grade inflammation, including adhesion molecules, were associated with greater arterial stiffness over a six-year period.[26] A causative effect of acute systemic inflammation on increasing large-artery stiffness and decrease in wave reflections was also shown in patients receiving vaccinations.[27]

Several mechanisms may explain the link between arterial stiffness and inflammation. First, degradation of the elastin and collagen of the vessel wall may be increased by activation of matrix metalloproteinases, which may be mediated by increased levels of inflammatory mediators, including adhesion molecules.[11] Inflammation may also provoke fibrosis and smooth muscle proliferation, which would subsequently cause arterial stiffness.[11]

Another possible explanation is the major role of the endothelium in arterial stiffness. Inflammation causes endothelial dysfunction and alters arterial distensibility by impairing the production of vasodilatory factors.[27] One last, speculative explanation could be arterial stiffness causing inflammation, since elevated pulse pressure and increased shear stress may stimulate inflammation and increase the expression of adhesion molecules.[20,22,28]

Conclusion

We were unable to find a significant correlation between aortic stiffness and circulating adhesion molecules (VCAM-1 and ICAM-1). Possible causes of this finding have been discussed above. However, other factors may have affected the results. The mean age in our study was 55.6 ± 10.5 years. Since arterial stiffening typically occurs after the age of 60 years, our study population represented a relatively young population.[26] Second, arterial stiffening is not a uniform condition in all arterial systems, and aortic distensibility is a local measure of arterial stiffness.[22] Third, levels of adhesion molecules were measured only once, and they may be subject to intra-individual variability. The small study size is another limitation of this study.

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Redo off-pump coronary artery bypass grafting via a left thoracotomy

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Abstract

Background: In this study, we retrospectively reviewed our experience in a meticulously selected group of patients undergoing redo off-pump coronary artery bypass graft (CABG) surgery from the descending aorta to the circumflex artery (Cx) and its branches.

Methods: Between January 2001 and October 2013, 32 patients at our hospital underwent redo off-pump CABG from the descending aorta to the Cx and its branches via a left posterolateral thoracotomy. Of these patients, 27 were male (84.3%) and five were female (15.7%), with a mean age of 61.66 ± 8.63 years. All patients had a patent left internal thoracic artery-to-left anterior descending coronary artery (LITA–LAD) anastomosis. Thoracotomy was performed through the fifth intercostal space. The saphenous vein or radial artery was prepared as a graft at the same time as the left posterolateral thoracotomy from the contralateral extremity, without any positional problem.

Results: The main reasons for surgery in this group of patients were new lesion formation in 19, graft occlusion in six, and both in seven patients. The average operating time was 143.90 ± 36.93 minutes, respiratory assist time was 5.08 ± 1.88 hours, intensive care unit (ICU) stay was 21.3 ± 4.41 hours and hospital stay was 5.06 ± 2.74 days. Thirty-eight bypasses were performed. The follow-up period was 56.17 ± 39.2 months. Six patients were lost in the follow-up period and four patients died. Twenty-two were alive and free of cardiac problems.

Conclusion: Redo off-pump CABG via a left posterolateral thoracotomy provided a safe and effective surgical approach with lower rates of postoperative morbidity and mortality in patients who required revascularisation of the Cx and its branches.

Keywords: coronary artery bypass grafting, re-operation, circumflex artery, thoracotomy

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Re-operative coronary artery bypass graft (CABG) surgery is more complicated than the initial CABG and it may also be more hazardous because of risk factors related to median resternotomy, such as cardiac injury and damage to the patent grafts due to sternal adhesion.[1] Deciding on the appropriate treatment for recurrent coronary artery disease (CAD), especially conditions such as non-left anterior descending coronary artery (LAD) ischaemic lesions during the existence of patent left internal thoracic artery-to-left anterior descending coronary artery (LITA–LAD) anastomosis is a dilemma.[2]

If the patient is unresponsive to medical therapy, and percutaneous transluminal coronary angioplasty (PTCA) and/or stenting is not appropriate for revascularisation, alternative surgical strategies, excluding resternotomy and cardiopulmonary bypass (CPB), may be the most appropriate way of revascularising the branches of the circumflex artery (Cx) or right coronary arteries (RCA) (non-LAD territories).[3-5] In selected patients, off-pump redo CABG for the branches of the Cx via a posterolateral thoracotomy may reduce the risks due to median resternotomy and dissection of the heart.

This procedure to avoid resternotomy and CPB has become an established and popular way of revascularising recurrent coronary artery disease in the lateral aspect of the heart. In this article, we share our experience of 32 patients who underwent redo CABG for the Cx and its branches via a left posterolateral thoracotomy.

Methods

Between January 2001 and October 2013, 32 off-pump CABG re-operations via a posterolateral thoracotomy for the branches of the Cx system were performed at the Department of Cardiac Surgery of Guven Hospital in Ankara, Turkey. During this time, 450 patients underwent isolated redo off-pump CABG and our study group constituted 7.1% of this population. There were 27 men and five women, aged 61.66 ± 8.63 years, with a mean of 40–76 years (Table 1).

Co-morbidity factors of the patients were pre-operative hyperlipidaemia, family history, smoking, hypertension, diabetes mellitus, chronic obstructive pulmonary disease and cerebrovascular disease. The period between the first and redo operation via thoracotomy was 103.03 ± 63.33 months (20–264). Only one patient was operated on three times, the others were operated on twice. There were 2.16 ± 1.019 anastomoses performed in each of the previous operations and the total number of anastomoses was 67, whereas the number of patent anastomoses was 44. All of the LITA-to-LAD anastomoses were patent and 10 of the RCA and two of the Cx system anastomoses were also patent.

Patients had symptoms of angina, depending on a problem in the Cx system, and unfortunately medical therapy was unsuccessful. Six had already been revascularised by both PTCA

Table 1. Pre-operative demographic data

Variables	*Demographic data* (n = *32*)
Age (years) (mean)	61.66 ± 8.63 (40–76)
Male, *n* (%)	27 (84.4)
Female, *n* (%)	5 (15.6)
Hypertension, *n* (%)	21 (65.6)
Smoking, *n* (%)	21 (65.6)
Diabetes mellitus, *n* (%)	13 (40.6)
Family history, *n* (%)	22 (68.7)
Hyperlipidaemia, *n* (%)	22 (68.7)
Myocardial infarction, *n* (%)	11 (34.3)
COPD, *n* (%)	6 (18.7)
CVA, *n* (%)	2 (6.2)

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident.

Table 2. Information on the patients after the first operation up to the redo Cx CABG via thoracotomy

Variable	*Number ± SD*
Number of previous grafts	2.1667 ± 1.019
Patent anastomoses	
LIMA–LAD	32
RCA	10
Cx	2
Reason of redo Cx CABG	
Graft occlusion	6
New lesion	19
Both	7
Interventions	
PTCA	4
PTCA + stent	6
Period between the first and redo CABG via thoracotomy operation (months)	103.03 ± 63.33

and stent. PTCA only was performed in four of the patients. Complete revascularisation is the first priority universally for all patients in cardiac surgery, so these were all candidates for redo CABG. The reason for ischaemic symptoms in six of our patients was graft occlusion, new lesions in 19, and both in seven (Table 2). New lesions occurred in the left main coronary arteries of eight patients (Fig. 1), and in the rest, in branches of the Cx.

We decided to perform an off-pump posterolateral thoracotomy for redo CABG in these patients because of the presence of patent grafts (Fig. 2), to avoid the risks of resternotomy, and to access the posterior region of the heart more easily while revascularising the branches of the Cx system. One of the most significant independent predictors of morbidity and mortality after redo CABG is reported to be long duration of CPB.[6] We therefore decided to avoid CPB and chose the off-pump redo CABG technique via a thoracotomy for revascularising the lateral aspect of the heart.

All patients underwent redo off-pump CABG via a left posterolateral thoracotomy (Fig. 3) with general anaesthesia after insertion of a double-lumen endotracheal tube. The patient was positioned in the right lateral decubitus position with the pelvis externally rotated slightly to allow access to the femoral vessels for cannulating the patient if necessary. The saphenous veins (SV) or radial arteries (RA) were prepared as grafts at the same time as the thoracotomy, from the contralateral extremity, without any positional problems. A supine position before thoracotomy was necessary in only one patient for harvesting the SV because the right SV had been harvested before. In six patients, the SV was harvested and in the rest the RA was used.

A left posterolateral thoracotomy was performed through the fifth intercostal space and adhesions of the collapsed left lung were dissected. After mobilisation of the left lung, the pericardium was opened above the target area, taking care with the phrenic nerve and LITA graft, which was patent in all our patients. We limited dissection of the adhesive tissues because extensive dissection may cause increased venous bleeding and a decrease in the natural stabilisation provided by the adhesions in redo CABG patients.[7]

After graft preparation, the proximal anastomosis was performed by placing a side-biting clamp on the descending aorta

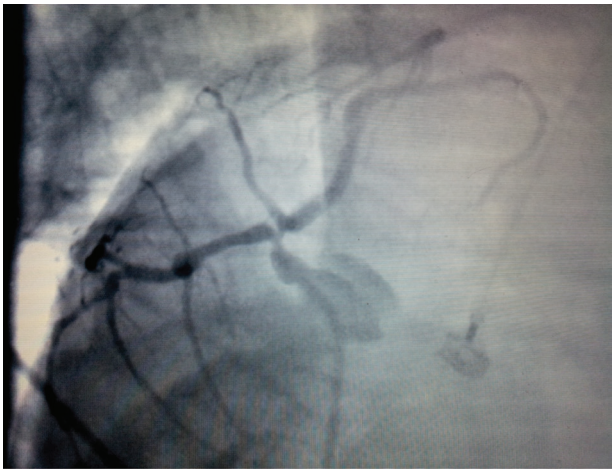

Fig. 1. New lesion in the left main coronary artery of a patient with a patent LITA–LAD anastomosis.

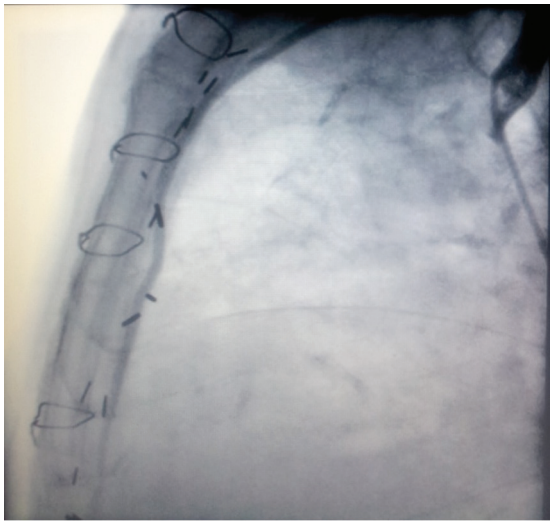

Fig. 2. Extremely adhesive LITA lying under the sternum, a good example of an indication for redo CABG via posterolateral thoracotomy.

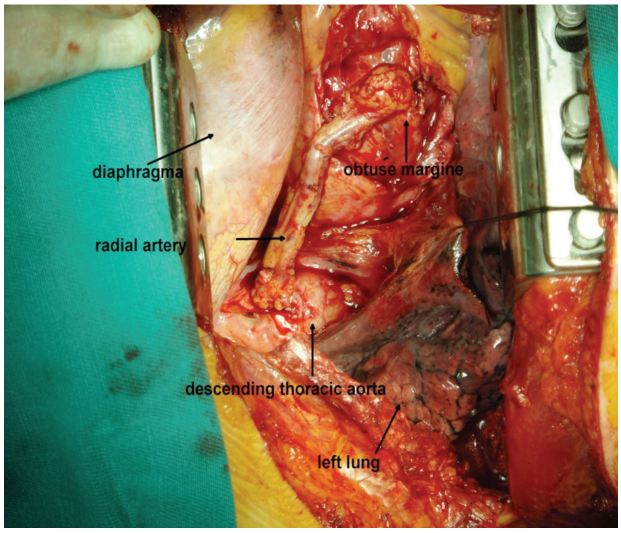

Fig. 3. Operative view of redo off-pump CABG for the obtuse marginalis branch of the Cx via a posterolateral thoracotomy.

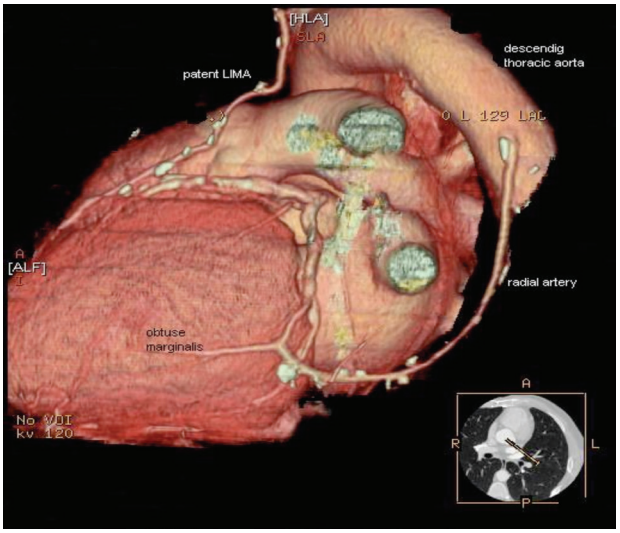

Fig. 4. The radial artery was anastomosed between the descending thoracic aorta and obtuse marginalis branch of the Cx without any kinking.

in a continuous fashion with a 7-0 polypropylene suture. The descending aorta was used for the inflow in all patients. When the target vessel was identified posterolaterally, four stabilising sutures were placed at each corner.[8] After arteriotomy, to achieve a comfortable distal anastomosis, a fine vascular occlusion clamp was used to stop bleeding and the distal anastomosis was performed continuously with an 8-0 polypropylene suture. The position and length of the graft was controlled meticulously to protect it from kinking (Fig. 4).[9]

Results

All operations were performed without CPB and electively via thoracotomy. None required conversion to resternotomy or institution of CPB. The average surgery time was 143.90 ± 36.93 minutes. The number of anastamoses was 1.1875 ± 0.39 per patient (38/32). Average ICU stay was 21.3 ± 4.41 hours with 5.08 ± 1.88 hours of respiratory assist, and drainage was 497.65 ± 291.43 ml. Average hospital stay was 5.06 ± 2.74 days (Table 3).

Table 3. Operative findings

Variables	*Mean (n = 32)*	*Min*	*Max*
Operation time (min)	143.90 ± 36.93	90	270
Drainage (ml)	497.65 ± 291.43	100	1550
Number of anastomoses	1.1875 ± 0.39	1	2
Respiratory assist (h)	5.08 ± 1.88	2	10
ICU stay (h)	21.3 ± 4.41	14	36
Hospital stay (days)	5.06 ± 2.74	4	18
Mortality	0		
Early complications			
Myocardial infarction	0		
Use of IABP	0		
(+) inotrope	1		
Atrial fibrillation	1		
Deep-vein thrombosis	1		
Thoracotomy incision infection	1		
Revision for bleeding	1		
Follow up (months)	56.17 ± 39.20	1	152
Alive and well	22		
Lost to follow up	6		
Dead	4		

The follow-up period was 56.17 ± 39.2 months (1–152) post-operatively. Twenty-two of 32 patients were alive and well, six patients were lost in the follow-up period and four patients died. There was no in-hospital mortality. All were discharged free of angina. No peri-operative myocardial infarction was observed, none of our patients required intra-aortic balloon pump (IABP) and no renal failure occurred. One patient recovered with the help of positive inotropic support. Atrial fibrillation developed in one patient, deep-vein thrombosis in another, and infection occurred in the thoracotomy incision scar of a third patient. Unfortunately one patient underwent a revision because of bleeding.

Discussion

Redo CABG presents challenges that initial CABG surgery does not pose. Re-operative technique and the deteriorating condition of these patients cause raised morbidity and mortality rates of re-operated patients compared with the initial CABG patients.[6] The most serious complications in isolated redo CABG are massive haemorrhage, injury to patent LITA grafts, and embolisation of the patent but very atherosclerotic ascending aorta and old venous grafts due to median resternotomy and extensive dissection of the heart.[10-12]

Recurrent coronary artery patients who are candidates for re-operation tend to be affected more negatively by the deleterious effects of CPB because of their decreased capacity for cardiac contractility.[6] Off-pump redo CABG revascularising the Cx and its branches via a left posterolateral thoracotomy in carefully selected patients presents dramatically improved consequences as a result of avoiding median resternotomy and CPB.[5,13,14]

In our clinic, selected candidates for this procedure are patients suffering from angina due to lesions in the Cx and its branches, who are non-responsive to medical therapy and/or with failure of PTCA/stent. All must have patent LITA–LAD anastomoses. Other indications mentioned in the literature for this procedure are: calcified ascending but not descending aorta, sternum osteomyelitis or mediastinitis, mediastinal irradiation, requirement of concomitant left lung surgery, and previous mitral valve replacement, which creates a risk for atrioventricular groove rupture while rotating the heart to approach the arteries from the lateral aspect.[15,16]

We believe that re-operative off-pump CABG, performed via a left posterolateral thoracotomy to revascularise the Cx and its branches eliminates the difficulties of median resternotomy, in addition to the potential negative effects of bleeding and embolisation due to cardiac and conduit injury during extensive dissection of the heart. Avoiding resternotomy and CPB in re-operative isolated CABG surgery decreases morbidity and mortality rates.[4,5]

Conclusion

In selected patients, off-pump re-operative CABG for the Cx and its branches via a left posterolateral thoracotomy can be performed with lower rates of morbidity and mortality in addition to cost-effective consequences.

This study was presented at the 23rd World Congress of the World Society of Cardiothoracic Surgeons, Split, from 12–15 September 2013.

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Social support and management of hypertension in south-west Nigeria

Pauline E Osamor

Abstract

Introduction: Social support can facilitate compliance or adherence to recommended treatment regimens, especially for chronic disease management. There is little data from Africa on the role of social support in the management of chronic disease.

Objective: The current study investigated the relationship between social support for treatment compliance among hypertensive subjects in a poor urban community in south-west Nigeria. A second objective was identifying the correlates of social support in the study sample.

Methods: The study was a community-based, cross-sectional and descriptive study of 440 community residents (mean age 60 years, 65.2% women) from Idikan community, Ibadan, Nigeria who had hypertension.

Results: Most subjects (~ 93%) reported receiving some social support from family members and approximately 55% reported receiving social support from friends. Social support from friends ($p < 0.0001$) but not from family ($p = 0.162$) was significantly associated with good compliance with treatment for hypertension. Factors associated with receiving significant support from both family and friends included marital status and religion, while age and educational level were associated with receiving significant support from family members only. Gender was not significantly associated with receiving social support.

Conclusion: We concluded that social support is strongly associated with hypertension treatment compliance in this community in south-west Nigeria. These findings suggest a need for exploring the promotion of social support as a useful tool in chronic disease treatment programmes.

Keywords: hypertension, social support, chronic disease, compliance, Nigeria, Africa

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The relationship between social support and health has been of great scientific interest for many years. Several epidemiological studies have pointed out the importance of social support for morbidity and mortality.[1] For mortality, there are consistent indications of a lower risk of death among people with a large social network.[2,3] This beneficial effect is confirmed for several morbidities, including cancer, coronary heart disease and other cardiovascular diseases (CVDs).[4,5]

Over the past quarter of a century, much research has convincingly documented the relationships between social networks and social support on morbidity, mortality, and a variety of positive chronic illness outcomes.[6,7] A number of behaviours or mechanisms may modulate the relationship between social support and self-management. For example, it is reasonable to assume that family members and friends may facilitate the self-management process in a variety of ways, providing, for example, occasional advice, emotional support, tangible support that indirectly facilitates self-management (e.g. shopping for heart-healthy food), and more direct assistance with illness-management activities.

There is some evidence that illness-specific support is more predictive of health outcomes than general support.[8] Therefore one might hypothesise that in the case of chronic illness self-management, illness-specific or regimen-specific support may have a stronger influence on self-management behaviour than more global types of support.

Rozanski, Blumenthal and Kaplan[9] reviewed 15 studies and found that people who reported low levels of social support were at greater risk of developing CVD. Blazer[10] published similar findings, indicating that low levels of perceived social support were found to be risk factors for developing cardiac events. Other research has suggested that adherence to drug therapy was strongly associated with family support provided to patients with hypertension.[11]

Hypertension is a major public health problem and a major risk factor for stroke, cardiac failure and chronic renal disease in developing countries. Currently, one-quarter of the world's adult population has hypertension, and modelled projections indicate an increase to 1.15 billion hypertensive patients by 2025 in developing countries.[12]

Several studies have examined the factors influencing compliance behaviours with hypertensive treatment. Among these studies, Marin-Reyes and Rodriguez-Moran[11] found that compliance with hypertensive treatment was directly linked to the support of family members.

It has been well documented that patients from disrupted or isolated social circumstances are less likely to be good compliers than those with stable families and/or helpful friends. However, only recently have there been systematic studies of attempts to engender or direct social support in order to improve compliance with antihypertensive therapy. These studies have not shown an independent effect on compliance of attempting to promote social support, but their results must be regarded as preliminary.

The present study investigated the influence of social support on treatment compliance among hypertensive subjects in a poor urban community in south-west Nigeria. A previous study[13] of the factors associated with hypertension treatment compliance in

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this community noted that having social support was associated with treatment compliance. In the present study, we proceeded to explore the issue of social support further by (1) exploring the relationship between social support and good compliance with treatment for hypertension, and (2) identifying factors associated with receiving social support from family and/or friends.

Methods

This descriptive study was conducted in Idikan community, Ibadan, a city in the south-western part of Nigeria, as part of a larger community-based study of the sociological aspects of hypertension. Ethical approval for the study was obtained from the joint University of Ibadan–University College Hospital ethical committee.

Idikan is located in the indigenous part of the city of Ibadan and has a population of 15 042.[14] The health facilities in the community include an outreach clinic run by the Department of Preventive Medicine and Primary Care of the University of Ibadan, four private clinics and a small dental clinic run by the Dental Centre of University College Hospital (UCH). There are over 150 registered patent medicine stores in the area. There are three traditional healing homes, and they are all accessible to members of the community.

The study was a descriptive, community-based, quantitative study of hypertensive subjects aged 25 years and above who were residents of Idikan community. Previous studies in the community[15,16] had conducted household screening for hypertension, which facilitated the identification of hypertensive subjects in the community. The subjects for this study were selected from a list of known hypertensive subjects residing in the community that was developed from one such previous hypertension study and updated for the present study during home visits.

Four hundred and forty hypertensive subjects were enrolled using a consecutive sampling method. After obtaining informed consent, subjects were administered a semi-structured questionnaire that had items on several issues, including healthcare seeking for hypertension, their beliefs about hypertension, compliance with treatment, and availability of social support (from family and friends).

Social support for compliance was assessed in the structured questionnaire using the questions: (1) Do you normally seek financial support from family members for your hypertension? (2) How concerned are your family members about your hypertension? (3) How interested are your friends in talking with you about your hypertension? (4) How helpful are your family in reminding you to take your hypertension medication? (5) How helpful are your friends in reminding you to take your hypertension medication? Social support from family members or friends was defined as reporting support from family as 'helpful' or 'very helpful' in being concerned about respondents' hypertension (non-directive support), and reminding of medication (directive support).

As previously described[13] compliance was defined using the question on how frequently people missed taking their medication. The use of compliance as a variable was defined by first scaling compliance as 'good' or 'high compliance' (where the respondent 'never misses' or 'rarely misses' taking his/her medication doses), 'medium compliance' (where the respondent 'sometimes misses' taking medication) and 'poor' or 'low compliance' (where the respondent 'regularly misses' or 'fairly regularly misses' taking the medication. Since the desired goal of treatment for hypertension is that the patient complies with taking medication in order to control the high blood pressure, we focused on 'good compliance' (where the respondent 'never misses' or 'rarely misses' taking his/her medication doses) as the main outcome variable to evaluate compliance in this study.

Statistical analysis

Management and analysis of the survey questionnaire data was done using SPSS version 11 (SPSS Inc, Chicago, USA). Frequencies of the responses to the questions were computed and presented as percentages. Association between categorical variables was tested using the Chi-square test.

Results

The 440 respondents comprised 65.2% women and 34.8% men. About half (51.1%) of the respondents had no formal education and half were traders. The ages of respondents ranged from 25 to 90 years, with a mean age of 60 (SD 12) years. Most (71%) of the respondents were married (Table 1). Most (70.0%) of the respondents knew about their hypertensive condition only when they were invited to participate in a research study, during which their blood pressure was measured, while 23.0% of the respondents found out that they were hypertensive when they were ill with some other ailment and went to hospital for treatment. The most common perceived causes of hypertension were anxiety (35.7%) and stress (25.2%), followed by mental illness (7.5%) and 'unhappiness' (5.5%).

The majority (77.5%) of the respondents claimed they complied with keeping their follow-up clinic appointments every time, and 46% said they were on medication at the time of the study. Roughly one-half (50.7%) of respondents had good compliance with treatment as they claimed to be taking their medication regularly, whereas 41.5% had poor compliance at different levels, ranging from regularly missing taking their medication to rarely taking their medication.

Social support and treatment compliance

Having a family member with hypertension was significantly associated ($p = 0.038$) with compliance in general with 49.3% of those who said 'yes' versus 61.7% of those who answered 'no'. Overall, 85 (19.3%) of the respondents reported that family members were very concerned about their hypertension while 329 (74.8%) said family members were extremely concerned about their hypertension. Also, 89 (20.2%) and 322 (73.2%), respectively, reported that family members were very helpful or extremely helpful in reminding them about taking their medication.

Regarding support from friends, 116 (26.4%) of respondents reported that friends were very concerned about their hypertension while 127 (28.9%) said family members were extremely concerned about their hypertension. Ninety-one (20.7%) and 150 (34.1%) respectively reported that family members were very helpful or extremely helpful in reminding them about taking their medication.

Both having a family member with hypertension and having

Table 1. Demographic characteristics of respondents

Characteristic	*Number*	*Percentage*
Smoking	15	3.4
Alcohol use		
Beer	10	2.3
Wine	13	3.0
Whisky	10	2.3
Other liquor	8	1.8
Religion		
Islam	270	61.4
Christianity	169	38.4
Traditional	1	0.2
Ethnic group		
Yoruba	434	98.6
Ibo	5	1.2
Isoko	1	0.2
Educational level		
No formal education	225	51.1
Primary education	86	19.5
Secondary education	49	11.1
Post-secondary education	77	17.5
Other (Arabic school)	3	0.7
Occupation		
Trading	220	50.0
Artisan	49	11.1
Teaching/civil servant	43	9.8
Retired/not working	113	25.7
Religious teachers	15	3.4
Taking antihypertensive medication	257	58.5

Table 2. The association between social support and good treatment compliance in hypertension

		Good compliance		
Variable	*Response*	n *(%)*	χ^2	p
Has a family member with hypertension	Yes	36 (49.3)	6.233	0.044*
	No	206 (61.7)		
	Don't know	15 (45.5)		
Has a family member who has serious health problems from hypertension	Yes	12 (36.4)	9.064	0.011*
	No	230 (61.2)		
	Don't know	15 (48.4)		
Family members concerned about respondents hypertension	Not very	10 (47.6)	4.128	0.248
	Don't know	43 (50.6)		
	Very	201 (61.1)		
	Extremely	3 (60.0)		
Family members helpful in reminding about medication	Not very	12 (54.6)	5.132	0.162
	Don't know	43 (48.3)		
	Very	198 (61.5)		
	Extremely	4 (57.1)		
Friends concerned about respondent's hypertension	Not very	95 (49.0)	35.700	< 0.0001*
	Don't know	59 (50.9)		
	Very	102 (80.3)		
	Extremely	1 (33.3)		
Friends helpful in reminding about medication	Not very	96 (49.2)	41.738	< 0.0001*
	Don't know	40 (44.0)		
	Very	119 (79.3)		
	Extremely	2 (50.0)		

*$p < 0.05$.

a family member who had suffered complications were not associated with good compliance. On the other hand, having friends who were concerned about the respondent's hypertension or who were helpful in reminding the respondent about taking medication were associated with good compliance. A higher proportion of those whose friends were very concerned about their hypertension reported good compliance than those who did not get such support from their friends ($p \leq 0.0001$). Similarly, a higher proportion of respondents whose friends were very helpful in reminding them about their hypertension medication reported good compliance than those who did not get such support from their friends ($p \leq 0.0001$) (Table 2).

Factors associated with receiving social support

Having found a significant association between some aspects of social support (from friends) and good treatment compliance, we investigated socio-demographic factors influencing receiving social support. As shown in Table 3, a higher proportion of older respondents (> 55 years) rather than younger respondents reported receiving social support from family ($p < 0.0001$). Gender was not significantly associated with respondents getting social support. On the other hand, there was a significant association between those who were currently married at the time of the study and support from family ($p = 0.0006$) and support from friends ($p = 0.009$).

It is of interest also to note that both religion and educational level of respondents were significantly associated with getting social support from both family and friends. A higher proportion of respondents of the Islamic faith (in contrast to Christians) received social support from family and friends, respectively, while respondents with no formal education (in contrast to those with some education) received social support from members of their families.

Discussion

Social support is a construct that describes the structure of a person's social environment and the tangible, instrumental and emotional resources the social environment provides. A wealth of data, particularly from large, long-term, observational studies, has shown that higher levels of social support, whether measured by instrumental, tangible or emotional indices, are associated with reduced cardiovascular morbidity and mortality.[9,17-19] The disease-related protective effects of social support were first described in the 1970s.[20] From that time, there has been great interest in the relationship of social support to health, and in particular to cardiovascular disease.[21] However, there is scarcity of such studies from Africa.

The issue of social support for health issues in African societies warrants close study, given some of the characteristics of these societies. For example, there is an emphasis on the family and community rather than the individual, and many individuals live in extended (rather than nuclear) family set-ups. This often means that an individual's problems (including health issues) are not his/hers alone but that of the family. On the other hand, individuals may conceal medical diagnoses for various reasons (e.g. stigma, fear of being considered 'different' or of the family being perceived as 'tainted' or cursed), which means family members and friends may be unaware and cannot provide support.

Table 3. Social demographic characteristics and receiving social support among Nigerians with hypertension

Characteristic	n	*Support+ from family* n *(%)*	χ^2 *(p-value)*	*Support+ from friends* n *(%)*	χ^2 *(p-value)*
Age group					
25–55 years	171	101 (59.1)	37.28	58 (33.9)	0.11
> 55 years	223	223 (85.1)	($p \leq 0.001$)*	93 (35.5)	($p = 0.736$)
Gender					
Male	137	99 (72.3)	1.34	56 (40.9)	3.17
Female	275	213 (77.5)	($p = 0.247$)	88 (32.0)	($p = 0.075$)
Current marital status					
Unmarried	128	219 (70.2)	11.93	121 (38.8)	6.74
Married	312	110 (85.9)	($p = 0.0006$)*	33 (25.8)	($p = 0.009$)*
Religion					
Islam	270	217 (80.1)	10.51	108 (39.9)	7.30
Christianity	169	112 (66.3)	($p = 0.001$)*	46 (27.2)	($p = 0.007$)*
Educational level					
No formal education	225	190 (84.4)	22.83	77 (34.2)	0.12
Some education	215	139 (64.7)	($p \leq 0.001$)*	77 (35.8)	($p = 0.726$)

+Support defined as being 'helpful' or 'very helpful' in reminding of medication. *$p < 0.05$.

In Ushie and Jegede's study[22] on the paradox of family support, concerns of tuberculosis-infected HIV patients about involving family and friends in their treatment reported that family support was *expressly* seen by participants as central to medication adherence but one of the main drawbacks to its maximal utilisation was fear of condemnation and stigma from family members and friends, and from the family as a whole, which makes people with HIV and/or TB hide their status.

Chronic illnesses that require life-long treatment (such as hypertension and diabetes) pose unique challenges in such a context, not least of which is the need to maintain the motivation to adhere to treatment for many years. The need to understand social support in such a context was the primary motivation of this study.

In the present study, those who had support from friends or family members (concerned about their illness, giving reminders about medication) showed better treatment compliance than those who did not, although this difference was greatest for those who had the support of friends. This is an important finding and is consistent with what has been reported for multiple chronic diseases in several parts of the world.[23,24] Interestingly, the evidence from this study shows that support from friends is a stronger factor influencing good compliance than support from family members.

By contrast, Marin-Reyes and Rodriguez-Moran[11] found that compliance with hypertensive treatment was directly linked to the support of family members. The findings of the present study may be a reflection of the fact that most people in this urban community (and in cities in general) talk and interact more with their friends than with their family members who do not live nearby. In this regard, it would be important to study people who live in rural areas where living in extended-family and multi-generational households is more common. Another explanation may be that those with hypertension are more likely to discuss their health problems with their friends than with family members, thereby inadvertently limiting the support they could receive from the latter.

Given the role played by social support in compliance with hypertension treatment in this community, it was instructive to attempt to identify the factors associated with receiving such support. While a specific subset of factors (demographic factors) was explored in this study, age, marital status, religion and educational level were each associated with receiving social support. Each of these factors is noteworthy. However, it is difficult to evaluate how demographic factors interact with the larger set of factors known to be associated with social support. For example, it is known that marked cultural differences exist in the types and effectiveness of social support, as well as in how people use their support networks.[23] These cultural differences may underlie some or most of the apparent relationships with demographic factors observed in this study.

The findings of this study suggest ways in which social support could be used in the treatment of hypertension in this community. First, it would seem that adding social support to treatment guidelines could improve awareness by healthcare providers of this important component of treatment compliance. Second, teaching health providers how to explore and utilise their patients' social support networks may help to improve treatment compliance. Third, exploring the use of existing social networks (e.g. peer groups, cultural groups, religious groups) in this and similar communities may impact on how social support can be leveraged to improve health behaviours.

To our knowledge, this is the first study focused on social support with regard to treatment compliance in hypertension or cardiovascular disease in Nigeria. The strengths of the study include a large sample size, focus on a single non-communicable condition, which limits heterogeneity from differing diseases and their treatments, and a community-based design, which better permits generalisation than a hospital-based design. Limitations include a cross-sectional design, which does not permit identification of cause and effect, and the use of self-report measures.

However, this was an exploratory study and more studies are needed to confirm and extend the findings. Such studies should be designed to ameliorate or overcome the limitations of the present study, including the use of more comprehensive and validated social support assessment tools, collecting more variables on each subject, inclusion of qualitative methods, and

the development of mechanisms/models of social support and their role in health behaviours.

Conclusion

We concluded that social support is strongly associated with hypertension treatment compliance in this community in south-west Nigeria. These findings suggest a need for exploring the promotion of social support as a useful tool in chronic disease treatment programmes.

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Comparison between superficial femoral artery stenting and bypass surgery in severe lower-limb ischaemia: a retrospective study

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Abstract

Background: Symptomatic femoro-popliteal disease is treated by bypass surgery or angioplasty with or without stenting. The aim of this study was to compare the results of stenting and bypass surgery with regard to limb salvage in patients with severe leg ischaemia.

Methods: A total of 213 patients with femoro-popliteal disease presenting with severe claudication or critical limb ischaemia between January 2009 and December 2013 were evaluated; 118 patients (139 limbs) had stents placed and 95 patients (104 limbs) had bypass surgery. Most (60%) presented with critical limb ischaemia (rest pain 40%, tissue necrosis 20%), and the remainder with severe claudication. The treatment groups had matching risk factors.

Results: The average age was 66 years and 73% were male. Tissue necrosis was found in 26% of the stent group and 12% of the bypass group ($p = 0.009$). In the stent group 26% had adjunctive procedures, compared to 16% in the bypass group ($p = 0.138$). During the one-year follow up, there were 30 stent occlusions (22%) and 18 graft occlusions (17%) ($p = 0.42$). There were 14 major amputations (10%) in the stent group, and 13 (13%) in the bypass group ($p = 0.68$). Limb salvage rate was 90% in the stent group, and 88% in the bypass group ($p = 0.68$). There were no peri-operative deaths in the stent group, but one in the bypass group (1%). One-year mortality rate was equal (8%) in both groups ($p = 1.00$).

Conclusion: One-year outcome was comparable in both groups with regard to mortality, stent or graft patency and limb salvage rates.

Keywords: superficial femoral artery, stenting, bypass, severe leg ischaemia

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Symptomatic superficial femoral artery (SFA) disease presenting either with severe claudication or critical limb ischaemia is treated with bypass surgery and traditionally has been the 'gold-standard' procedure. Surgical bypass using autogenous vein or prosthetic grafts as a conduit is well accepted and there are comparable patencies and limb salvage rates with either conduit.[1]

There have been considerable advances in the last two decades in percutaneous endovascular technology for the treatment of SFA disease. The techniques that have been developed include percutaneous balloon angioplasty and stenting, with variable results.[2,3] Despite having three different options, namely surgical bypass, balloon angioplasty and stenting, none is superior to the other.

Although the five-year primary patency rate of femoro-popliteal above-the-knee bypass with autogenous saphenous vein is 70%, this method of treatment is invasive with long incisions in the lower extremities and a peri-operative complication rate of 12%.[4] Vascular surgeons have become more experienced with catheter-based technology and due to the minimal invasiveness of the procedure, both patients and vascular surgeons are increasingly attracted to endovascular procedures. Mwipatayi *et al*.[5] and Nguyen *et al*.[6] found stenting resulted in equivalent outcomes when compared to balloon angioplasty alone, but Laird *et al*.[7] found that self-expanding nitinol stents were associated with better angiographic results and improved patency compared with balloon angioplasty alone.

Randomised, controlled trials comparing bypass surgery and balloon angioplasty alone generally showed similar outcomes in terms of amputation-free survival but in the short term, surgery was more expensive than angioplasty.[8] Another study comparing surgical bypass with balloon angioplasty and stenting showed better primary patency for the stent group (67%) than the bypass group (49%) and there were higher re-intervention rates in the bypass group.[9]

Since there are conflicting data in the literature regarding the success of different methods of treatment of SFA disease and there is a lack of consensus guidelines on the optimum management of SFA disease, the aim of this study was to compare the results of stenting and surgical bypass in the local environment with regard to limb salvage rates in patients with severe leg ischaemia.

Methods

Patients with superficial femoral artery (femoro-popliteal) disease presenting to a single practice, with severe claudication (crippling), preventing them from performing their daily activities, or critical limb ischaemia, admitted to Entabeni Hospital, Durban, South Africa between January 2009 and December 2013 were culled from a prospectively maintained database. Two

hundred and thirteen (213) patients were evaluated; 118 patients (139 limbs) had had stents placed and 95 (104 limbs) had had bypass surgery. We did not include patients who had had balloon angioplasty alone.

Most of the patients (60%) presented with critical limb ischaemia and the remainder with crippling claudication. Among the patients with critical limb ischaemia, 40% presented with rest pain and the remainder with tissue necrosis (20%). Both treatment groups had similar risk factors. Follow up comprised clinical review at one month, six months and yearly thereafter.

Stent treatment group

Due to the demand for minimally invasive procedures by patients, and the frequent presence of multiple co-morbidities in poor operative-risk patients, our practice has focused on an endovascular-first approach for most of the patients with less extensive lesions [TASC (Trans-Atlantic Inter-Society Consensus) IIA and B], reserving open surgical bypass for patients who had more extensive lesions (TASC IIC and D) or femoral artery origin disease.

All stenting was performed in a hybrid endovascular operating theatre with fixed imaging capabilities. In most cases, ipsilateral antegrade access was obtained with a 6-F sheath by percutaneous groin puncture. Distal run-off vessels were evaluated before crossing the lesions. All patients were given intravenous heparin (80 IU/kg).

Accurate measurement of lesion length and vessel diameter was obtained by calibration techniques. Lesions were crossed with a hydrophilic guide wire and an angled, tapered catheter, and the sub-intimal technique was used in some of the complete occlusive lesions.

All patients received a self-expanding uncovered nitinol stent from different manufacturers. More than one stent was used in some patients. All stents were ballooned post deployment. Post stent procedures, all patients received a loading dose of 300 mg of clopidogrel followed by 75 mg daily for four weeks, and were given aspirin and statin therapy on a long-term basis.

Bypass treatment group

Most bypasses were from the common femoral artery to above-the-knee popliteal artery, using polytetrafluoroethylene (PTFE) grafts. Reversed autogenous saphenous vein grafts were used when a suitable vein was available. All bypass grafts had a distaflo cuff configuration with ring reinforcement. Post operatively, all patients continued with aspirin and statin therapy on a long-term basis.

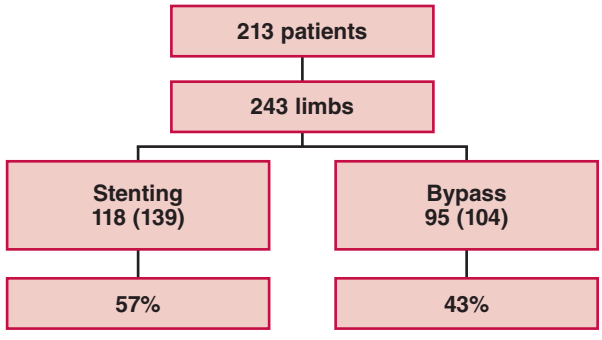

Fig. 1. Total patients and procedures.

Statistical analysis

In the case of quantitative data, means and 95% confidence intervals (95% CI) were reported around sample estimates. Fisher's exact test (two-tailed) and the *t*-test (two-tailed) were used for differences in proportions. A *p*-value of ≤ 0.05 was considered significant.

Results

Two hundred and forty-three limbs were treated in 213 patients. Stenting was done in 139 limbs (57%) and bypass in 104 limbs (43%) (Fig. 1). The average age of the patients was 66 years (95% CI: 64.66–67.17), 73% were male and the male-to-female ratio was 2.73. The average age was similar in both treatment groups: 67 years (95% CI: 65.01–68.75) in the stent group and 65 years (95% CI: 63.17–66.27) in the bypass group ($p = 0.08$). The stent group had a similar gender distribution compared to the whole group (69% male and 31% female), whereas the bypass group had more males (79%), however this difference was not statistically significant ($p = 0.11$).

Critical limb ischaemia (CLI) was the presenting symptom in the majority of patients [128 (60%)]. Of these, 86 patients (40%) presented with rest pain and 42 (20%) with tissue necrosis or gangrene. The remainder of the patients presented with severe claudication [85 (40%)]. The distribution of severe claudication and critical limb ischaemia was similar in both treatment groups (Table 1), except that more patients presented with tissue necrosis in the stent group (26%) compared with the bypass group (12%) ($p = 0.009$).

The prevalence of cardiovascular risk factors, for example hypertension, smoking, ischaemic heart disease (IHD), cerebrovascular disease (CVD), and renal failure was similar across the treatment groups, except for diabetes mellitus, which was higher in the stent group (51 vs 37%, $p = 0.05$), as shown in Table 2. The presentations according to the TASC II classification are shown in Table 3. Overall, 80% of TASC A and TASC B lesions received stents and 76% of TASC C and D lesions received bypass ($p = 0.0001$). In the stent group 26% of patients had adjunctive procedures, compared to 16% in the bypass group ($p = 0.138$) (Table 4).

During the one-year follow-up period there were 30 stent occlusions (22%). They were treated by balloon angioplasty alone (three patients), re-stenting (11), femoro-popliteal bypass (13), and three patients were treated conservatively. In the bypass group 18 patients had graft occlusions (17%) and they were

Table 1. Clinical presentation

	Stent n *(%)*	*Bypass* n *(%)*	p-*value*
Severe claudication	42 (36)	43 (45)	0.16
Rest pain	45 (38)	41 (43)	0.48
Tissue necrosis	31 (26)	11 (12)	0.009
Total	118 (100)	95 (100)	

Percentage rounded to the nearest integer.

Table 2. Demography and risk factors

	Stent (n = *118*) n *(%)*	*Bypass* (n = *95*) n *(%)*	p-*value*
Age (years)	67	65	0.08
Males	81 (69)	75 (79)	0.11
Hypertension	85 (72)	63 (66)	0.37
Diabetes	60 (51)	35 (37)	0.05
Smoking	65 (55)	51 (54)	0.89
IHD	45 (38)	30 (32)	0.38
CVD	12 (10)	12 (13)	0.66
Renal failure	9 (8)	6 (6)	0.79

IHD: ischaemic heart disease, CVD: cerebrovascular disease.
Percentage rounded to the nearest integer.

managed by thrombectomy, angioplasty with or without stenting (five), or redo bypass (nine). Four septic grafts were removed.

There were 14 major amputations (10%) in the stent group and 13 (13%) in the bypass group (p = 0.68). The limb salvage rate was 90% in the stent group and 88% in the bypass group (p = 0.68). There were no peri-operative (30-day) deaths in the stent group, but one peri-operative death after discharge home due to an unknown cause in the bypass group (1%). One-year mortality rate was equal (8%) in both groups (p = 1.00), as shown in Table 5. The causes of late deaths were myocardial infarction (10) and sepsis (two). In five patients the cause of death remained obscure.

Discussion

All of our patients treated by endovascular techniques received a stent in addition to angioplasty. This is different from that reported in the BASIL (Bypass versus Angioplasty in Severe Ischaemia of the Leg) trial where patients in the endovascular group underwent angioplasty alone.[8] During the same time period we had another 30 patients, who had balloon angioplasty done alone for the SFA disease, but we did not include them in this study, as we feel that balloon angioplasty and stenting have different results in terms of patency. This may differ from other authors.[10]

Stenting is appropriate for complex lesions and as a 'bail-out' procedure after complications of balloon angioplasty, or recoil after balloon dilatation, and the outcome with stenting is superior to balloon angioplasty alone.[6,7,11] We did not give preference to any specific stent, and a single stent was preferred in order to cover the entire lesion; multiple stents were however deployed if necessary.

In all cases, bare-metal, self-expanding nitinol stents were used. It has been reported that long-term outcomes of SFA intervention comparing endografts and bare-metal nitinol stents were similar.[12] The average lesion length was 7.84 cm (range 4 to 20 cm) and the stent diameters ranged from 5 to 7 mm.

Eighty-six limbs (83%) had above-the-knee bypass, all using prosthetic grafts. Below-the-knee bypass was done in 18 (17%); a prosthetic graft was used in 14 of these and reversed saphenous vein grafts were used in four patients.

Although in one study the five-year patency and re-intervention rates were superior in above-the-knee bypass with saphenous vein grafts,[13] other randomised, controlled trials showed that the outcome in terms of patency and limb salvage rates were comparable.[1,4] Below-the-knee bypass with vein grafts is definitely superior to prosthetic grafts.[14] Lack of availability of suitable veins precluded their use, and we were compelled to use prosthetic grafts in most cases.

Out of 86 above-the-knee prosthetic bypasses, 11 had a major amputation and of 18 below-the-knee bypasses, two resulted in amputation. Though no patient with a vein graft had an amputation, this was not statistically significant (p = 1.00).

The difference between stent and graft occlusion rates was not statistically significant (22 vs 17%, p = 0.42), and the stent and graft patency rates were similar in both groups: 109 (78%) in the stent group and 86 (83%) in the bypass group (p = 0.42). There was no difference in the major amputation rate between stents and bypasses, with 14 amputations (10%) in the stent group and 13 (13%) in the bypass group (p = 0.68). Among the patients who had amputation, 93% had presented with tissue necrosis in the stent group, and 46% in the bypass group (p = 0.01). The limb salvage rate was similar in both groups; 125 (90%) in the stent group and 91 (88%) in the bypass group (p = 0.68).

One-year mortality rate was similar in both groups; 10 (8%) in the stent group and eight (8%) in the bypass group (p = 1.00). The causes of late deaths were similar to previous reports, being mainly due to myocardial infarction. The current report was limited to a one-year follow up. This might have been responsible for the higher stent and graft patency, or limb salvage rates in comparison to other series.[9,15] No patients were lost to follow up.

There are not many publications comparing femoral artery stenting and bypass surgery, and the assessment of patency and the overall results of different treatment modalities is somewhat problematic, as study designs vary considerably.[16-19] In our series,

Table 4. Adjunctive procedures

	Stent	*Bypass*	p-*value*
Popliteal-tibial angioplasty	22	0	
Iliac angioplasty/stenting	5	15	
CFA patch	4	0	
Total	31 (26%)	15 (16%)	0.13

CFA: common femoral artery.

Table 3. TASC II lesions

TASC II	*Number (%)*	*Stent (%)*	*Bypass (%)*
A	46 (19)	43 (93)	3 (7)
B	97 (40)	72 (74)	25 (26)
C	24 (10)	13 (54)	11 (46)
D	76 (31)	11 (14)	65 (86)
Total	243	139	104

TASC: Trans-Atlantic Inter-Society Consensus.
Percentage rounded to the nearest integer.

Table 5. Outcomes after one year

	Stent (n = *139*) n *(%)*	*Bypass* (n = *104*) n *(%)*	p-*value*
Stent/graft occlusion	30 (22)	18 (17)	0.42
Major amputation	14 (10)	13 (13)	0.68
Death	10 (8)	8 (8)	1.00
Stent/graft patency rate	109 (78)	86 (83)	0.42
Limb salvage	125 (90)	91 (88)	0.68

Percentage rounded to the nearest integer.

80% of TASC II A and B lesions received stents and 76% of TASC II C and D lesions received bypasses. These figures are in keeping with those reported in previous studies.[9,18,19]

There is evidence that shorter lesions do well with angioplasty/stent, while longer lesions have significantly lower patency rates.[9] The latest TASC II recommendations include an endovascular approach for shorter lesions and a bypass for longer lesions.[20] We followed this principle in our practice. Our study design is similar to that of Malas *et al*.[9] and Linnakoski *et al*.[21] and the outcomes are comparable. Notwithstanding we support the concept that an endovascular-first approach may be advisable in the elderly and in patients with significant co-morbidity.[22,23]

Conclusion

Bearing in mind that this was a retrospective study, in the short term, stenting is a viable option to treat femoral artery occlusive disease. It is less invasive and equally effective compared to bypass surgery, especially in the elderly and in patients with high cardiovascular risk factors. One-year outcome was comparable in both groups with regard to mortality rate, stent or graft patency and limb salvage rates. There is a definite need for long-term follow up and a randomised, controlled trial to validate this.

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Study of the effect of altitude on the measurement of glycated haemoglobin using point-of-care instruments

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Abstract

We measured the glycated haemoglobin (HbA_{1c}) levels of a total of 24 non-diabetic volunteers and diabetic patients using a point-of-care (POC) analyser in three Cameroonian cities at different altitudes. Although 12 to 25% of duplicates had more than 0.5% (8 mmol/mol) difference across the sites, HbA_{1c} values correlated significantly (r = 0.89–0.96). Further calibration studies against gold-standard measures are warranted.

Keywords: glycated haemoglobin, altitude, diabetes

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HbA_{1c} concentration is used for the appropriate diagnosis and management of diabetes,[1,2] but the standard way of measurement requires an expensive and time-consuming ion-exchange, high-performance liquid chromatography (HPLC) technology. Point-of-care (POC) instruments represent a cheaper alternative to determine HbA_{1c} levels in five to 10 minutes. They can be used by non-laboratory staff to tailor a patient's care and educational messages to HbA_{1c} values and clinical findings in a one-stop-shop approach.[3,4] Their potential shortcomings include cases of haemoglobinopathy or some environmentally linked limitations.[5,6]

While operating temperature and humidity are easily controlled, altitude cannot be standardised for operation. We investigated the performance of one of the most commonly used POC HbA_{1c} instruments in African clinical settings, situated at varying altitudes.

Methods

In this cross-sectional study, HbA_{1c} concentrations were measured in three cities of Cameroon in blood samples simultaneously collected from the same individuals. The study settings were Douala (13-m altitude), Yaounde (650-m altitude), and Bamenda (1 600-m altitude).

The study was approved by the National Ethics Committee of Cameroon. All participants gave their informed consent.

The study participants were 24 volunteers distributed in four groups: six non-diabetic (healthy) volunteers [no clinical symptoms, fasting glycaemia < 1.26 g/dl (6.99 mmol/l) and HbA_{1c} levels < 6.6% (< 49 mmol/mol)], six patients with diabetes with HbA_{1c} levels < 6.6% (< 49 mmol/mol), six patients with HbA_{1c} levels at 6.6–8.0% (49–64 mmol/mol) and six patients with HbA_{1c} levels > 8.0% (> 64 mmol/mol).

All patients had to have had diabetes for at least one year, with stable treatment and HbA_{1c} values over at least three months preceding the study defined by HbA_{1c} variation < 1% between two measurements. Exclusion criteria included any haemoglobinopathy, recent malaria, haematological disorder or any other acute medical condition in the preceding month, total haemoglobin level > 11 g/dl, and creatinine clearance < 60 ml/min.

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Volunteers were invited, and after informed consent, we conducted an interview, clinical examination and biochemical investigations for the ascertainment of eligibility. Collections of venous blood in eligible participants were all done the same day from an antecubital vein in four EDTA tubes stored in refrigerated containers for all three assays.

The blood samples collected on the same day for each participant were immediately transported by car to the target settings in a refrigerated container. The room temperature was standardised for all study sites at 25°C, and humidity was maintained between 45 and 60%.

HbA_{1c} measurements were performed using the In2it POC device (Bio-Rad laboratories, Deeside, UK), which was calibrated prior to the study, with all reagents from the same lot (072T128). The same operator performed the assays in each of the settings within 48 hours of blood collection. All manipulations were done following the operating procedure of the manufacturer in order to reduce the variability of the measurements.

Statistical analysis

Using SPSS 17.0, data were analysed and expressed as mean ± standard deviation. Comparisons across the groups were done using analysis of variance, and associations were verified by Spearman's correlation. Agreement between methods was assessed using Bland and Altman plots of the difference against the means of the two methods.

Results

Participants were 12 males and 12 females, aged 54 ± 15 years. Their mean body mass index was 28.9 ± 5.8 kg/m^2, mean systolic and diastolic blood pressures were 128 ± 18 and 77 ± 8 mmHg, respectively, and mean haemoglobin was 13.4 ± 1.8 g/dl. The duration of diabetes in all patients was 10 ± 6 years with a pre-inclusion HbA_{1c} value of 7.8 ± 2.3%.

Overall, there was no statistically significant difference between mean HbA_{1c} measurements across the sites (Table 1). The correlation between measurements varied from $r = 0.89$, $p < 0.001$ between the 650-m/1 600-m altitudes, $r = 0.92$, $p < 0.001$ between the 13-m/650-m altitudes, to $r = 0.96$, $p < 0.001$ between 13-m/1 600-m altitudes. The coefficient of variation (CV) was 3.4% for the 650-m/13-m duplicates, 5.1% for 1 600-m/13-m duplicates and 3.2% for 1 600-m/650-m duplicates.

Table 1. Comparison of mean HbA_{1c} levels by group across the sites

	Point-of-care In2it analyser			
Study group	*Douala (13 m)*	*Yaounde (650 m)*	*Bamenda (1 600 m)*	p-*value*
Healthy controls	5.0 ± 0.6	5.4 ± 0.3	5.6 ± 0.5	0.15
Patients with diabetes				
HbA_{1c} < 6.5% (< 49 mmol/mol)	5.9 ± 0.6	5.7 ± 0.6	5.9 ± 0.4	0.29
HbA_{1c} 6.5–8.0% (49–64 mmol/mol)	8.1 ± 3.0	7.9 ± 3.1	8.0 ± 3.0	0.66
HbA_{1c} > 8.0% (> 64 mmol/mol)	8.4 ± 1.8	8.5 ± 1.7	9.0 ± 2.2	0.84
All study participants	6.8 ± 2.2	6.9 ± 2.2	7.1 ± 2.3	0.31

The mean differences expressed as estimates (95% CI) in percentages between measurements at two different sites were –0.04 (–1.05−0.97%), +0.14 (0.95−1.24%) and +0.13 (–0.45−0.70%), respectively, between the 650-m/13-m (Fig. 1A), 1 600-m/650-m (Fig. 1B), and 1 600-m/13-m altitudes (Fig. 1C).

The HbA_{1c} differences were > 0.5% (8 mmol/mol) in 3/24 (12%) between the 1 600-m/13-m measurements, 4/24 (17%) between the 650-m/13-m measurements and in 6/24 (25%) between the 1 600-m/650-m measurements. In only one case associated with more than one percentage difference across sites was a patient with one of the readings at 4.2% (22 mmol/mol) in one site, which normally would have prompted a second check. We did not find any differences in the percentage variation of HbA_{1c} levels at the low ($n = 12$), medium ($n = 6$) and high ($n = 6$) values for the different study sites, namely 650-m/13-m ($p = 0.453$), 1 600-m/650-m ($p = 0.111$) and 1 600-m/13-m altitudes ($p = 0.344$).

Discussion

This study indicates that the POC analyser showed no significant differences across Cameroonian sites located at altitudes varying from 13 to 1 600 m (≤ 0.5% in 75% of comparisons). Although measurements were not repeated in each site to reflect clinical practice, our results suggest a test reliability of the In2it POC instrument below 1 600 m.

Interestingly, previous studies in which the device calibration was performed with HPLC, had suggested satisfactory external validity.[7] This was however not investigated in our study and therefore represents a major limitation with the sample size.

However, considering our findings and the cut-off value of 3.5% of CV for optimal performance between laboratories (between study sites in our case), one could say that although

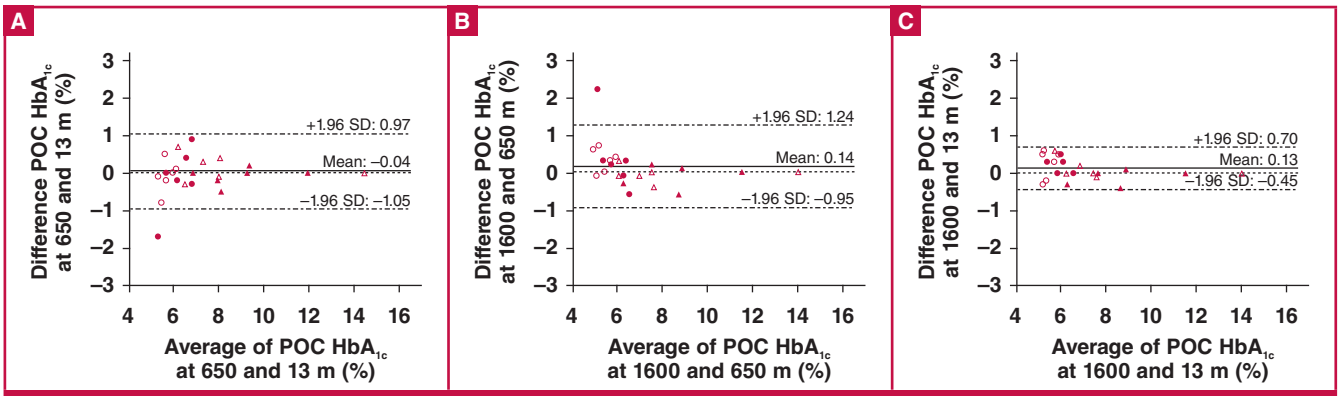

Fig. 1. Plots of the differences against averages of POC HbA_{1c} levels at 13-m and 650-m altitudes (A), 1 600-m and 650-m altitudes (B), and a1 600-m and 13-m altitudes (C), with mean difference (bias) and 95% agreement limits.

no significant difference was observed between HbA_{1c} levels at the three altitudes, the POC apparatus had a relatively high variability between 13 and 1 600 m.[8] As expected, this variability was higher in low and normal HbA_{1c} levels (not shown).

In this regard, the use of the POC HbA_{1c} analyser could be more indicated for the monitoring of patients with a view to comparing before- and after-treatment glucose control, especially in the lower values, even in the absence of calibration with an HPLC machine.

Consistent with our results, a recent study of HbA_{1c} variations in Chinese populations living at different altitudes did not find meaningful variations in the HbA_{1c} levels and the estimated average glucose levels of patients living in different sites.[9]

However, on the one hand, Ju *et al.*[9] in their study used the immunoturbidimetric method for the measurement of HbA_{1c} levels (also without validation against the gold standard for HbA_{1c} measurement), while we used a baronate affinity chromatography to separate glycated from non-glycated haemoglobin for photometry.[4,9] On the other hand, we sought to evaluate the possible effect of altitude on the accuracy of a POC HbA_{1c} analyser in patients with diabetes, while they aimed to evaluate whether altitude could modify the glycation of HbA_{1c}.

In our study, we observed that 12–25% of duplicates had more than a 0.5% (8 mmol/mol) difference across the sites. The performance of POC apparatus in general and the In2it in particular has (independent of altitude) been assessed before. These investigations constituted a body of evidence showing the need for improvement in the performance of devices for optimal care.[10-12]

The recent performance of these devices has given promising results. This also was the case where the In2it apparatus is concerned, despite the between-batch variability of results, which still needs to be addressed.[7,13] To circumvent this in our study, we used reagents from the same lot number at all study sites. However, in daily clinical practice, this could indeed be a concern for patients' follow up.

With the generalisation of HbA_{1c} use, especially in developing countries that have limited access to an HPLC and have a wide variety of physical environments, it is important to know which parameters should be taken into account when validating POC HbA_{1c} devices, which are commonly presented as the adequate alternative to estimate glycaemic control of patients.

Conclusion

Our results reinforce the need for calibration of POC instruments against the HPLC in each setting used, to ensure validity of the readings. We did not find any significant differences when measuring HbA_{1c} levels at different altitudes on the same samples. However this requires validation with further studies, using larger sample sizes and addressing situations with higher proportions of patients with haematological disorders.

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U-vein compressor improves early haemodynamic outcomes in radiocephalic arterio-venous fistulae in under 2-mm superficial veins

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Abstract

Aim: In this study, we sought to determine the early post-operative results of arterio-venous fistulae (AVF) created by U-vein compressors with veins between 1.5 and 2 mm in size.
Methods: Pre-operative venous mapping was done. The fistula tract was marked at 0-, 4-, 8- and 12-cm points; 0 cm was the estimated point where the anastomosis would be done. With Doppler ultrasonography, transverse diameters in the estimated fistula tract were measured at the 0-, 4-, 8- and 12-cm points. A superficial vein that would be used as the fistula tract was dilated using U-vein compressors. In the first postoperative hour, the flow in the anastomosis, and the transverse diameter of the fistula tract at the 0-, 4-, 8- and 12-cm points were measured by Doppler ultrasonography.
Results: Forty patients were included in the study. U-vein compressors were used for 20 patients. Postoperative expansion of vein diameters and postoperative flow velocities were found to be statistically significantly different in patients where a U-vein compressor had been used ($p < 0.001$).
Conclusion: We present a technique to dilate veins that are between 1.5 and 2 mm in diameter, which are generally accepted as poor vessels to create radiocephalic arterio-venous fistulae.

Keywords: arterio-venous fistula, vein diameter, flow, maturation

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The radiocephalic arterio-venous fistula (RCAVF) has remained the access point for maintenance haemodialysis because of its low incidence of complications and high long-term patency rate. Distal radial-cephalic anastomosis just above the wrist is still the best site for an arterio-venous fistula (AVF). This provides a relatively long, straight cephalic vein for catheter insertion. It also leaves more proximal sites for future use should the radial-cephalic fistula fail.

A 'failure-to-mature' AVF is caused by intrinsically poor native vessels. Poor native vessels relate to the use of a suboptimal artery or vein to create the AVF.[1]

Methods

Between January 2010 and April 2012, 40 normotensive patients (mean age 56.8 years, range 47–69), 22 males and 18 females, who underwent RCAVF (20 patients by standard technique, 20 by modified technique) were included in this study. The following inclusion criteria were considered before access placement: (1) the non-dominant arm should be selected (if possible), (2) the access should be placed distally in the forearm, (3) the selected veins in the forearm should have a long segment to allow for variation in puncture sites and should have a diameter between 1.5 and 2 mm. Exclusion criteria were: (1) atherosclerotic or calcific arteries, (2) redo operations, (3) hypotensive patients.

Pre-operatively, venous mapping was done on all patients. The fistula tract was marked at 0-, 4-, 8- and 12-cm points (Fig. 1); 0 cm was the estimated point where the anastomosis would be done. With Doppler ultrasonography, the arterial and venous systems were examined and transverse diameters were measured at the 0-, 4-, 8- and 12-cm points.

All operations were done under local anaesthesia. The cephalic vein was dissected surgically and freed in the distal forearm. Then distal end was ligated with a silk suture. An intravenous catheter was introduced through the proximal end of the vein and 2 500 IU of diluted heparin was transfused into the vein. For the standard technique (20 patients), a 10–12-mm arteriotomy was done in the radial artery and the cephalic vein was anastomosed end to side to the radial artery.

In the modified technique (20 patients), we used U-vein compressors manufactured from stainless steel, 3 cm in width and 5, 10 and 15 cm in length (Fig. 2). Here, a superficial vein that would be used as the fistula tract was dilated with the U-vein compressors by injecting a saline solution just after the intravenous catheter was introduced through the proximal end of the vein (Fig. 3). All sizes of U-vein compressors were used successively to dilate the vein gradually. The U-vein compressors occluded side branches and proximal segments of the cephalic vein externally. A 10–12-mm arteriotomy was placed in the radial

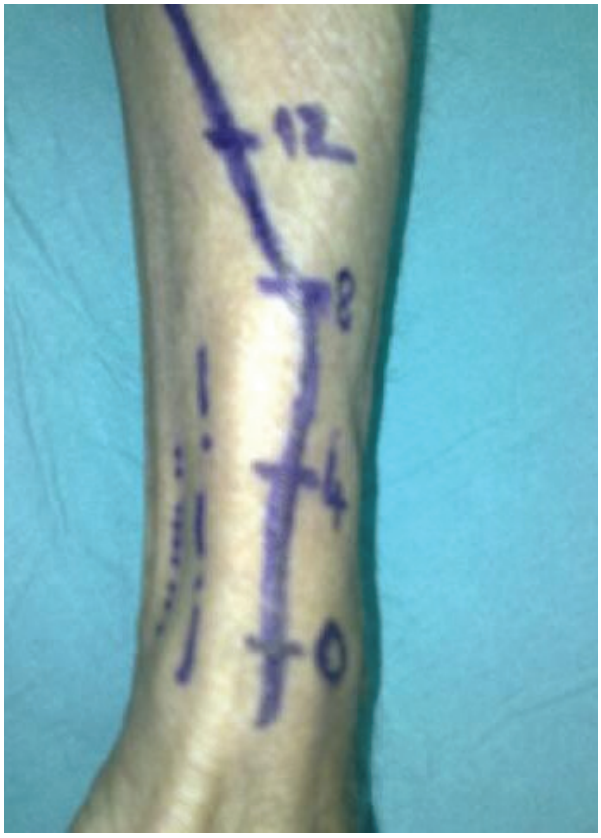

Fig. 1. Venous mapping.

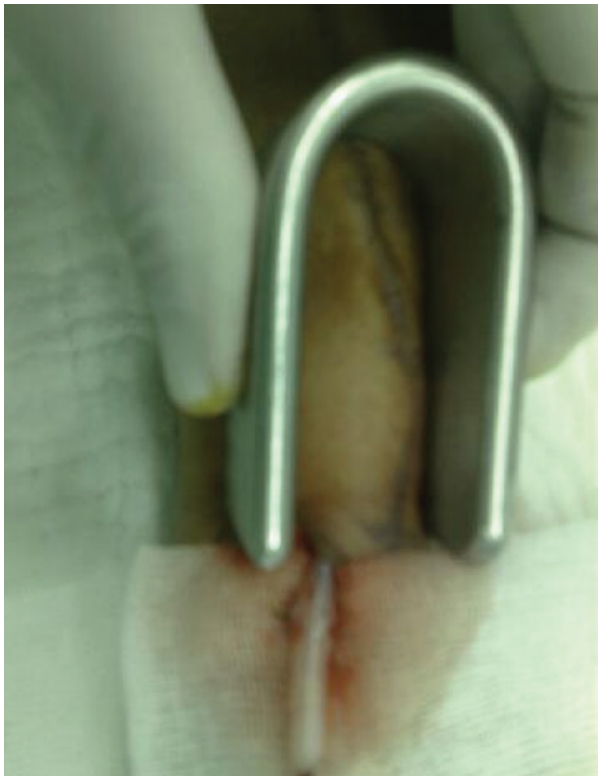

Fig. 3. Application of U-vein compressors, which were occluding the side branches and proximal segments of the cephalic vein externally.

Fig. 2. Stainless steel U-vein compressors. Their lengths were 5, 10 and 15 cm with a 3-cm width.

artery and the cephalic vein was anastomosed end to side to the radial artery.

Postoperatively, the presence of a trill in the arteriovenous fistula was examined by palpation. In the first postoperative hour, flow in the anastomosis and the transverse diameter of the fistula tract at the 0-, 4-, 8- and 12-cm points were measured with Doppler ultrasonography.

Statistical analysis

Statistical analyses were performed with SPSS 15.0 software (SPSS Inc, Chicago, IL). Forty patients were included in the analysis. Descriptive statistics are presented for numerical variables (mean, standard deviation, median, minimum and maximum). If the comparison of two independent groups of continuous variables provided the assumption of normality, the *t*-test was used. If it did not provide the assumption of normality, the Mann–Whitney *U*-test was used. The repeated-measures ANOVA test was used for repeated-measures statistics. All values of $p < 0.05$ were taken as significant.

Results

Forty patients were included in the study. Comparison of baseline clinical characteristics and pre-operative vein diameters between the two groups are shown in Table 1. U-vein compressors were used in one group of 20 patients (10 males, mean age 57.9 ± 8.12 years) and not in the other group of 20 patients (12 males, mean age 55.8 ± 7.52 years). There were no significant differences in

Table 1. Comparison of patients where U-vein compressors were not used and those where they were used

Variable	*Patients (U-vein compressor not used) (n = 20)*	*Patients (U-vein compressor used) (n = 20)*	p-*value**
Age (years)	55.8 ± 7.52	57.9 ± 8.12	0.41
Male, *n* (%)	12 (60)	10 (50)	0.53
Hypertension, *n* (%)	7 (35)	8 (40)	0.74
Hyperlipidaemia, *n* (%)	9 (45)	7 (35)	0.52
Chronic obstructive pulmonary disease, *n* (%)	5 (25)	6 (30)	0.72
Coronary artery disease, *n* (%)	7 (35)	6 (30)	0.74
Diabetes mellitus, *n* (%)	5 (25)	6 (30)	0.72
Current smoker, *n* (%)	5 (25)	6 (30)	0.72
Pre-operative vein diameter	1.77 ± 0.11	1.79 ± 0.12	0.71

Table 2. Comparison of pre- and postoperative diameters and postoperative flow velocity between patients where the U-vein compressor was not used and those where it was used

	Patients (U-vein compressor not used) (n = 20)	*Patients (U-vein compressor used) (n = 20)*	p-*value*
0 cm pre-operative	1.77 ± 0.11	1.79 ± 0.12	0.709
0 cm postoperative	2.45 ± 0.25	3.27 ± 0.42	< 0.001
4 cm pre-operative	1.78 ± 0.11	1.79 ± 0.11	0.832
4 cm postoperative	2.45 ± 0.25	3.27 ± 0.40	< 0.001
8 cm pre-operative	1.78 ± 0.11	1.81 ± 0.10	0.282
8 cm postoperative	2.47 ± 0.26	3.33 ± 0.38	< 0.001
12 cm pre-operative	1.79 ± 0.11	1.83 ± 0.10	0.307
12 cm postoperative	2.46 ± 0.26	3.33 ± 0.36	< 0.001
Flow velocity (postoperative)	197.15 ± 53.52	371.75 ± 93.98	< 0.001

age, gender, history of hypertension, hyperlipidaemia, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, current smoking status and pre-operative vein diameters between patients who were operated with and without the U-vein compressor.

There were no significant differences in the pre-operative diameters of the veins at the 0-, 4-, 8- and 12-cm points in the groups. Postoperative vein diameters in the patients where U-vein compressors were used were significantly greater at all points, compared with patients where it was not used ($p < 0.001$). Also, postoperative flow velocities were significantly higher in patients where U-vein compressors were used ($p < 0.001$) (Table 2).

In patients where the U-vein compressor was used, pre-operative mean transverse diameters (range 1.60–1.95 mm) at the 0-, 4-, 8- and 12-cm points were increased at least 75% postoperatively (range 2.80–3.90 mm). Flow measurements were between 326 and 670 ml/min.

Discussion

Endogenous AVF, first described in 1966, remains the optimal vascular access for chronic dialysis.[2] The RCAVF has remained the access for maintenance haemodialysis because of its low incidence of complications and high long-term patency rate.

An AVF within the anatomical snuffbox (triangular deepening on the radial, dorsal aspect of the hand) has a high incidence of early failure and requires a longer maturation time. The proximal elbow fistula predisposes to ischaemic complications and can lead to congestive heart failure as a result of increasing flow through a chronic fistula that is made too large. The distal radial–cephalic anastomosis just above the wrist is still the best site for an internal AVF. This provides a relatively long, straight cephalic vein for catheter insertion. It also leaves more proximal sites for future use should the RCAVF fail.

The fistula is allowed to mature for six to eight weeks prior to puncture. Occasionally longer periods of maturation are required to allow sufficient arterialisation of the vein, but if little venous distention is present at six weeks, either revision or an alternate access site is usually required. Having the patient perform repetative hand exercises such as squeezing a ball or a similar-sized compressable object may facilitate development of the outflow vein.

A failure-to-mature AVF is caused by intrinsically poor native vessels or by post-surgical derangements. Poor native vessels relate to the use of a suboptimal artery or vein to create the AVF. It has been noted that arteries less than 1.5 to 2 mm and veins less than 2 to 2.5 mm in diameter are associated with poor AVF maturation.[3-6] Silva *et al*. used a minimum of 2.5-mm vein size as predictable for fistula success.[1] In our technique, veins between 1.5 and 2 mm were associated with good AVF maturation by intra-operative use of a U-vein compressor.

Larger veins mean larger flow. However, such a simplistic view does not take into account arterial factors and normal pulsatile blood flow. Furthermore, venous compliance after fistula creation needs to be considered. In the study by Lauvao *et al*., eight patients with the smallest diameter between 1.5 and 2 mm on Doppler ultrasonograhy went on to develop mature fistulae, and three did not.[7] Their experience shows that vein size is the major predictor for a succesfull fistula.

In our study, pre-operative mean transverse diameters (range 1.60–1.95 mm) at the 0-, 4-, 8- and 12-cm points were increased at least 75% postoperatively (range 2.80–3.90 mm) and flow measurements were between 326 and 670 ml/min. The risk of failure was zero in the group where U-vein compressors were used, but the wrist radiocephalic arterio-venous fistula failed in six in the other group.

A well-functioning vascular access for haemodialysis plays a key role in the quality of life and clinical outcome of dialysis patients. Johnson *et al*. reported that a high intra-operative flow volume defined as 320 ml/min or greater was associated with a lower number of surgical revisions and longer access survival regardless of gender, race and the presence of diabetes.[8] The same authors reported that an intra-operative flow rate of less than 170 ml/min was correlated with a 56% risk for AVF failure within 50 days of construction.[8] A recent study including a cohort of 109 patients undergoing vascular access surgery for first-time haemodialysis showed that an intra-operative flow rate greater than 200 ml/min was associated with better mid-term outcomes in terms of requirement for revision and early patency rate.[9]

Fistula maturation is defined by the determination of both vascular surgeon and nephrologist that an access is patent and ready for cannulation based on adequency of blood flow through the fistula and adequency of vein dilatation in the 10-cm

segment.[7] In our technique, U-vein compressors were occluding side branches and proximal segments of the cephalic vein externally. The cephalic vein was dilated in the approximately 10–12-cm segment and its compliance was increased.

In most succesful AVFs, these flow and size parameters are generally met within the first few weeks of construction.[10] In our technique, these parameters (diameter and flow) are met in the first few minutes postoperatively because the superficial fistula tract is dilated enough during the operation by intra-operative use of the U-vein compressor.

We believe that this technique can maximise flow and minimise failure in AVFs using small, superficial veins. Postoperative hand exercises were not needed to accelerate maturation. This study needs long-term follow up but the technique we have described could be an alternative in patients with poor venous networks in the forearm.

Conclusion

In this article, we present a technique to dilate veins of between 1.5 and 2 mm in diameter, which are normally accepted as poor vessels to create RCAVF. With this technique, we can create good functioning arterio-venous fistulae in the early postoperative period, even if the superficial veins are not suitable for the standard technique. Our preliminary experience has shown satisfactory outcomes compared to the standard technique.

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The potential of low-carbohydrate diets to reduce cardiovascular risk

Consuming low-carbohydrate diets can reduce inflammation in patients with type 2 diabetes, which may decrease the risk of patients developing cardiovascular disease (CVD). According to a Swedish study [*Diabetologia* 2012; **55**(8): 2118–2127], eating a low-carbohydrate diet can reduce inflammation in patients with type 2 diabetes.

People with type 2 diabetes have a higher level of inflammation than those without diabetes, and this may play a role in the increased risk of CVD associated with diabetes. The Linkoping University study included 61 participants with type 2 diabetes. The participants were randomly divided up and given either a low-carbohydrate or low-fat diet. The study method was a retrospective follow-up study.

The low-carbohydrate and the low-fat diet participants were compared over the course of two years. Additionally, the researchers studied how the diets impacted on inflammation by checking the inflammation levels in the blood of each patient.

The results showed that both the low-carbohydrate and low-fat diets helped participants lose weight, roughly around nine pounds (four kg), but when it came to which diet produced reduced inflammatory markers in the blood, the low-carbohydrate diet succeeded. Additionally, glucose-levels dropped more in the low-carbohydrate diet groups.

In respect of cardiovascular risk, the researchers recommended aiming for a carbohydrate energy intake of 20% as a treatment alternative for at-risk patients.

Source

http://www.diabetesincontrol.com/articles/diabetes-news/16329-the-potential-of-low-carbohydrate-diets-to-reduce-cvd-risk.

An alternative method of transperitoneal graft introduction in aortobifemoral bypass surgery

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Abstract

Introduction: Intestinal injury and bleeding, which usually occurs while taking the graft through the transperitoneal tunnel, is one of the most important complications of aortobifemoral bypass surgery. In this study, case reports were examined where, for some reason, the tunneller instrument could not be used to create the transperitoneal tunnel and the tunnelling forceps was used. In some of these cases, the grafts were taken through conventionally and in others an alternative method was used.

Methods: Between 2002 and 2013, the records of 81 patients treated surgically by aortobifemoral bypass for peripheral arterial disease, were investigated retrospectively. In the conventional method, after creating a tunnel with tunnelling forceps, the forceps was re-introduced into the tunnel and the graft was clasped and brought through the tunnel. In the alternative method, a nylon tape was left as a guide in the tunnel while creating the tunnel, and the forceps was not introduced again. The graft was taken through the tunnel with the help of the nylon tape. Patients treated with the conventional method were included in group 1 (n = 49) and patients in which the graft was guided with nylon tape were included in group 2 (n = 32). The groups were compared peri-operatively.

Results: There were no significant differences between the groups in terms of co-morbidity factors. Extubation time, intensive care length of stay, revision for bleeding, other post-operative complications, and infection and late-term infection rates were similar in the two groups ($p > 0.05$). Hospital length of stay and blood usage were significantly higher in group 1 ($p < 0.05$). Drainage amounts were higher in group 1 but not statistically significant.

Conclusion: Using nylon tape to introduce the graft into the femoral area during aortobifemoral bypass operations was found to be more effective than using the tunnelling forceps.

Keywords: aortobifemoral bypass, tunnel, complication

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Aorto-iliac occlusive (AIO) disease is one of the most common forms of arteriosclerosis obliterans (ASO).[1] The gold-standard treatment of this disease is aortofemoral bypass surgery, according to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) study.[1-3]

Surgeons have performed this procedure for many years with good long-term results. Vascular damage, bleeding, intestinal damage, ileus, myocardial infarction and renal failure are considered short-term complications. Secondary aorto-enteric fistula, sexual dysfunction, infection, graft thrombosis and anastomotic pseudo-aneurysm may be considered long-term complications.[4-6] Among these complications, vascular damage, intestinal damage and aorto-enteric fistulae usually occur while introducing the graft into the femoral area.

If the tunneller, which was specifically designed for aortofemoral bypass procedures, is not available for some reason, long, blunt-tipped tunnelling forceps are used instead. A nylon tape is taken through the tunnel with the tunnelling forceps after the tunnel is created. Aortic anastomosis is performed after heparinisation.

Connecting the distal ends of the graft to the femoral area is performed in the conventional method by introducing the forceps into the tunnel a second time and pulling the graft through the tunnel. In an alternative method, the nylon tape that is taken through the tunnel with the tunnelling forceps is tied to the graft, which is pulled through into the femoral area. By not introducing the forceps a second time into the tunnel, complications caused by the forceps may be reduced. The results of both methods were analysed for postoperative bleeding, vascular injury and intestinal complications.

Methods

Between May 2002 and November 2013, 81 patients treated by aortobifemoral bypass (ABFB) via the transperitoneal approach for ASO were examined retrospectively. Parameters such as age, gender, pre-operative co-morbid factors, operative and postoperative data, and postoperative complications and death during follow up of all patients were recorded. Hospital records were used for obtaining the data.

Patients treated with the conventional method were included in group 1 (n = 49) and patients in whom the graft was introduced by means of the nylon tape were included in group 2 (n = 32). The group results were examined, comparing parameters such as pre-operative data and postoperative complications. Patients who previously had undergone abdominal surgery for any reason and who had had additional non-vascular abdominal surgery were excluded from the study.

The surgical indications were to relieve ischaemic pain, heal ischaemic ulcers, prevent limb loss, improve function and quality of life, and prolong survival, as described in the TASC II consensus. Digital subtraction angiography was performed on all patients to indicate the need for surgery.

Patients who had multiple risk factors and those who had symptoms of coronary artery disease (angina, ischaemic changes on electrocardiography, ischaemia on dipyridamole thallium scintigraphy, or left ventricular wall-motion abnormalities on stress echocardiography) were evaluated by means of pre-operative coronary angiography.

Coronary angiography was performed on three patients in group 1. Two of these patients were treated with angioplasty. In group 2, coronary angiography was performed on four patients and one required angioplasty. None of the patients required surgical intervention for coronary artery disease.

Mean follow-up time was 46.5 ± 27.7 (5–125) months in group 1 and 48.6 ± 29.6 (6–117) months in group 2. All operations were performed under general anaesthesia.

Surgical procedure in the conventional method

The femoral arteries were explored under the inguinal ligament and appropriate anastomosis sites were examined. The abdomen was explored with upper and lower median incisions. The abdominal aorta was explored and after deciding on the appropriate anastomosis site, the aorta was suspended with nylon tape.

Before heparinisation, transperitoneal tunnels were created between the femoral areas and the anastomosis site using a long, blunt-tipped forceps. A long nylon tape was transferred through the tunnel and left inside. After tunnelling, the patient was heparinised and the aortic anastomosis was performed. The nylon tape was then left and the previously created tunnel walls were stretched. Forceps were introduced a second time from the femoral area to the anastomosis site. The distal end of the graft was clasped and pulled through to the femoral area (Fig. 1). The same procedure was applied on the other side. Femoral anastomosis was performed and a drain was left intraperitoneally before closure.

Surgical procedure with nylon tape

The same procedure as in the conventional method was performed up to the aortic anastomosis. The distal ends of the graft were tied to the nylon tape and the aortic clamp was opened. The graft filled with blood. The femoral end of the nylon tape was pulled and the graft was introduced into the femoral area. The same procedure was applied for the other side (Figs 2, 3). Thereafter, the operation was continued as in the conventional method.

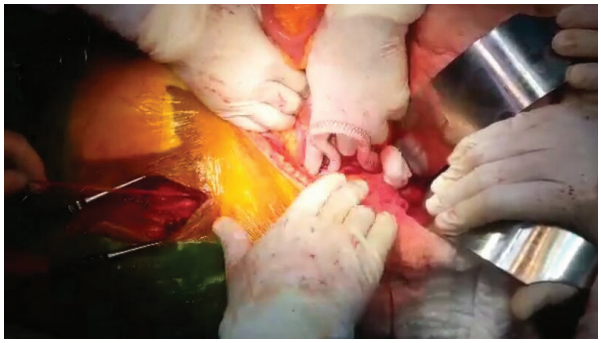

Fig. 2. The graft being pulled through with the nylon tape.

Results

The mean age was 60.98 ± 11.92 (37–92) years in group 1 and 62.88 ± 9.22 (43–81) years in group 2. There was no significant difference between the groups in terms of co-morbidity factors such as diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease and hyperlipidaemia ($p > 0.05$). Hypertension was significantly higher in group 2 patients ($p < 0.05$). Pre-operative data of both groups are summarised in Table 1.

When we compared operative data, we found that operation length was 246 ± 101.62 minutes in group 1 and 231.38 ± 65 minutes in group 2. Despite the operation length being shorter in group 2, it was not statistically significantly different ($p > 0.05$). There was no significant difference between the groups for additional vascular procedures. Operative data of the groups are summarised in Table 2.

When we compared postoperative data, there was no significant difference between the groups in terms of extubation time, intensive care length of stay, revision for bleeding, other postoperative complications [such as sexual dysfunction, nerve damage, secondary aorto-enteric fistula (SAEF), ileus, vascular injury or acute renal failure], infection and rehospitalisation for late-term infection ($p > 0.05$). Hospital length of stay and blood usage were significantly higher in group 1 ($p < 0.05$). Postoperative drainage levels were higher in group 1, but not statistically significantly different ($p > 0.05$) (Table 3). Mortality rates were similar in the two groups ($p > 0.05$).

In group 1, three patients died, two because of multiple organ failure and one because of myocardial infarction at late term. In group 2, two patients died, both because of multiple organ failure.

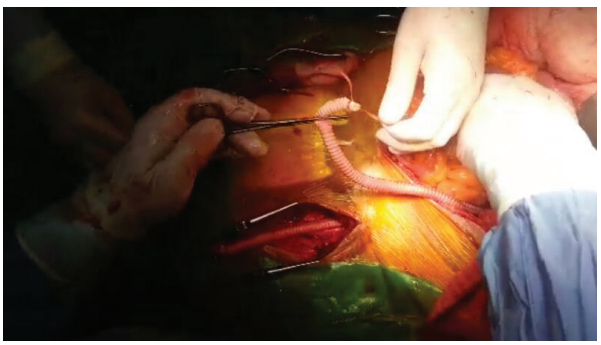

Fig. 1. The graft tied to the nylon tape.

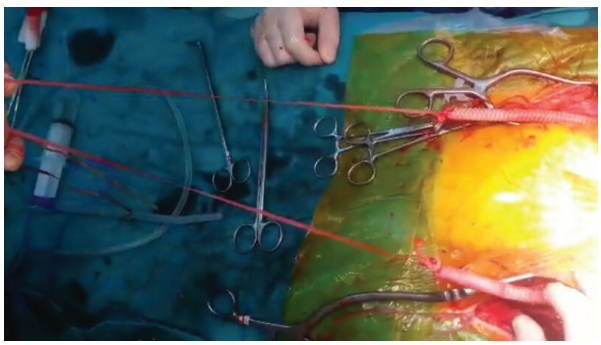

Fig. 3. After transferal of the graft using the nylon tape.

Table 1. Pre-operative data of patients

Parameters	*Group 1*	*Group 2*	p-*value*
Age (years)	60.98 ± 11.92	62.88 ± 9.22	0.448
Females	5 (10.2)	2 (6.3)	0.698
Diabetes mellitus, *n* (%)	15 (30.6)	12 (37.5)	0.520
Hypertension, *n* (%)	22 (44.9)	22 (68.8)	0.035
Chronic obstructive pulmonary disease, *n* (%)	7 (14.3)	7 (21.9)	0.377
Hyperlipidaemia, *n* (%)	18 (36.7)	18 (56.3)	0.084

Discussion

The gold-standard treatment for aorto-iliac occlusive disease is ABFB. This procedure has been performed for many years with good long-term results. Despite many modifications for reducing complications (retroperitoneal approach and minimally invasive approach), the transperitoneal approach is still the most widely used technique.[1,7]

Many studies have proved that the minimally invasive approach has advantages for cardiac risk, postoperative complications and postoperative ileus, but a randomised, prospective study did not prove any significant advantage over the conventional technique.[1] The minimally invasive approach is advised for patients with previous abdominal surgery or co-morbidities, and the elderly.

In this study, we preferred the conventional approach. There were some complications of ABFB with the conventional approach, which may have been specific to the surgery, such as SAEF, vascular injury, bleeding, intestinal injury, ileus, myocardial infarction, renal failure, sexual dysfunction, infection, graft thrombosis, anastomotic pseudo-aneurysm (which may differ in different abdominal approaches), or non-specific complications such as myocardial infarction, pulmonary complications and renal dysfunction.[1,4-7]

Chiu *et al.* revealed that, although there were different rates of complications in different series, rates were approximately 16% in their review.[8] The rates ranged between 0 and 11% in other reviews.[8-12]

Postoperative bleeding is a common early complication and causes re-operation in 1–2% of patients.[13] Inadequate control of bleeding, anastomotic technique, intra-operative use of heparin, and dilutional coagulopathy occurring after blood loss have been shown to be the most common causes of this complication.[13]

Another complication in the postoperative period is acute renal failure. Declamping and lack of fluid balance are thought to be the cause of this complication.[13] Mortality rates in our study were 6.15% in group 1 and 6.3% in group 2, which was similar to that in the literature.

Complication rates (excluding death) were 15% in group 1 and 10% in group 2. Acute renal failure was found in only one patient in group 2. Bleeding requiring re-operation was found in seven patients in group 1 and one in group 2. SAEF, rarely seen in our series but commonly encountered in the literature, was not observed in any of our patients. Inferior vena cava injury, termed vascular injury, was seen in two patients in group 1 but none in group 2.

Table 2. Operative data of patients

Parameters	*Group 1*	*Group 2*	p-*value*
Operation length (min)	246.1 ± 101.62	231.38 ± 65	0.490
Additional vascular procedures, *n* (%)	17 (35)	12 (38)	0.789
Embolectomy, *n* (%)	4 (8)	3 (9)	
Endarterectomy, *n* (%)	4 (8)	4 (13)	
Femoropopliteal bypass, *n* (%)	9 (19)	5 (16)	

Table 3. Postoperative data of patients

Parameters	*Group 1* (n = *49*)	*Group 2* (n = *32*)	p-*value*
Extubation time (hours)*	15.07 ± 9.73	16.3 ± 12.61	0.975
Intensive care length of stay (days)*	2.30 ± 1.26	2.25 ± 1.04	0.940
Hospital length of stay (days)*	6.92 ± 1.81	6.09 1.86	0.039
Revision for bleeding, *n* (%)	7 (15)	1 (3)	0.137
Other complications, *n* (%)*			0.731
Ileus	7 (15)	3 (10)	
Inferior vena cava injury	5 (11)	2 (7)	
Acute renal failure	2 (4)	1 (3)	
Postoperative infection, *n* (%)	7 (15.2)	6 (20)	0.588
Postoperative drainage (ml)	490 ± 613	257 ± 318	0.219
Postoperative blood product usage (units)	4.02 ± 2.87	2.04 ± 2.01	0.042
30-day mortality	3 (6.1)	2 (6.3)	0.981

*Parameters of the deceased patients were excluded from the calculation.

We believe some of the complications seen in other cases may have been associated with manipulation by the tunneller during surgery. A study by Luo and colleagues, comprising a case report accompanied by a literature review, is one of the studies supporting our theory.[14]

In our study, the tunneller was not used and forceps were introduced into the tunnel a second time in the conventional method. Postoperative bleeding amounts were higher but not statistically significant in the conventional method. Peri-operative blood usage was significantly higher in the conventional method. Although it was not statistically significant, ileus rates were higher in the conventional method. This situation may have been related to longer hospital stay due to bleeding.

Our study has some limitations. Group sizes were particularly small and graft patency data were not obtained for all patients.

Conclusion

Some complications of ABFB, which are directly related to the surgery, may be avoided, especially in cases where the tunneller is not used. Nylon tapes that are left in the tunnel while creating it may be used to introduce the distal end of the graft into the femoral area. This alternative method must be kept in mind as it has lower complication rates than the conventional method.

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Case Report

Five-year follow up of Konno aortoventriculoplasty for repeat aortic valve replacement in an adult patient

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Abstract

Konno aortoventriculoplasty (AVP) is performed for various types of left ventricular outflow tract obstruction. We report on a 32-year-old woman who had undergone double valve replacement five years earlier. She presented with increased interventricular septum thickness, small aortic root and gradient across the aortic mechanical valve. We performed Konno AVP with repeat aortic valve replacement (AVR). The control echocardiography showed no significant residual gradient. Konno AVP with repeat AVR may be safely performed with satisfactory results.

Keywords: aortic valve replacement, aortoventriculoplasty, Konno, re-operation

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Aortoventriculoplasty (AVP), also known as the Konno procedure since initial descriptions of the technique in 1975,[1] has proven to be safe and effective in relieving complex left ventricular outflow tract (LVOT) obstruction in a number of studies.[2,3] This procedure allows one to enlarge the aortic root and increase the size of the aortic valve implanted.

In this report, we present five-year follow up of our experience with the use of the anterior root-enlargement technique (Konno AVP) in conjunction with repeat aortic valve replacement (AVR) in an adult who had undergone mitral valve replacement (MVR) and AVR five years earlier.

Case report

A 32-year-old woman had had AVR (size no 19, St Jude Medical, Inc, St Paul, MN) and MVR (size no 23, St Jude Medical, Inc, St Paul, MN) due to rheumatic heart disease five years earlier. She was admitted to our clinic with a month's history of fatigue, dyspnoea, initially on intense effort and subsequently on minimal exertion. The symptoms had worsened during the last few days, leading to dyspnoea at rest with features of orthopnoea, coughing with foamy expectoration, weakness and coldness. She was classified as New York Heart Association (NYHA) functional class III.

On examination, cardiac auscultation revealed a reduced second sound with no aortic closing click. Transthoracic (TTE) and transoesophageal (TEE) echocardiographies revealed increased interventricular septum thickness (17 mm), small aortic root [1.9 cm (< 1 cm/m^2)] and gradient across the aortic mechanical valve (mean: 55 mmHg, peak: 110 mmHg), and ejection fraction (EF) was 56%. The mechanical mitral valve function was normal. We chose to perform the Konno AVP on this patient.

Re-operation was performed via repeat median sternotomy. Standard cardiopulmonary bypass (CPB) was established with aortic and both vena caval cannulation. The ascending aorta and pulmonary trunk were dissected and the position of the right coronary artery was accurately identified. Systemic hypothermia was maintained at 28°C and intermittent potassium-enriched cold blood cardioplegia was used.

A vertical aortotomy was made and the valve was inspected. After explanting the old valve substitute, excessive fibrotic tissue was debrided. To relieve subvalvar obstruction and to implant a new, larger prosthesis, an incision was made in the right ventricular outflow tract, followed by an incision across the aortic annulus into the ventricular septum to the left of the right coronary artery ostium, as described by Konno *et al*.[4] (Fig. 1).

A Dacron patch was tailored to fit the enlargement, approximately 2 × 4 cm, and was positioned on the right side of the septal opening, increasing the annular circumference of 1.5 cm. A no 23 St Jude (St Jude Medical, Inc, St Paul, MN) valve was then inserted on the patient's annulus and its Dacron extension (Fig. 2). After valve insertion, the Dacron patch was used for ascending aorta enlargement. Finally, the right ventricular outflow tract was closed with a Dacron patch (Fig. 3).

The postoperative course was uneventful. An electrocardiogram showed sinus rhythm. On follow-up transthoracic TTE, the gradient across the LVOT was below 20 mmHg and on the mitral mechanical valve, the peak gradient was 4 mmHg.

The patient was discharged on the tenth postoperative day. She was anticoagulated with warfarin, keeping the international normalised ratio (INR) between 2.5 and 3.5.

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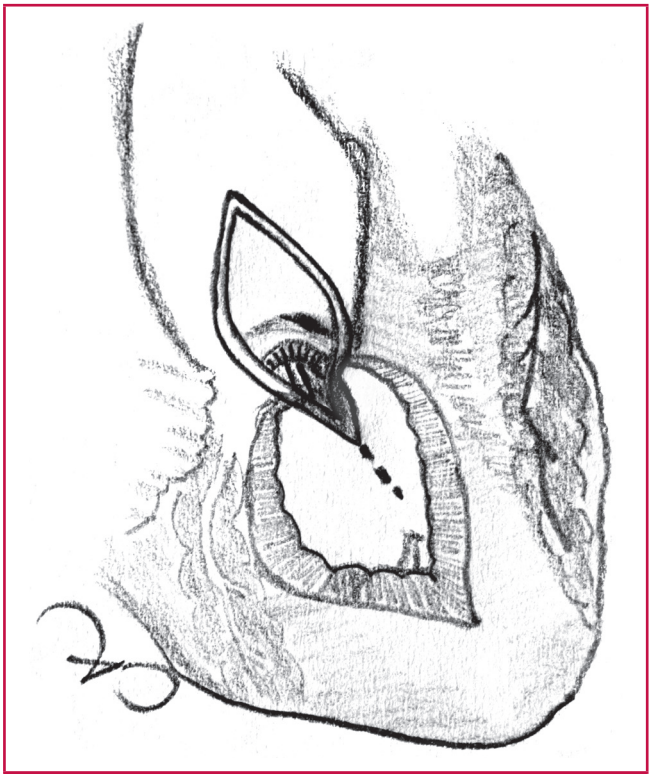

Fig. 1. Vertical aortatomy, incision in the right ventricular outflow tract and the ventricular septum.

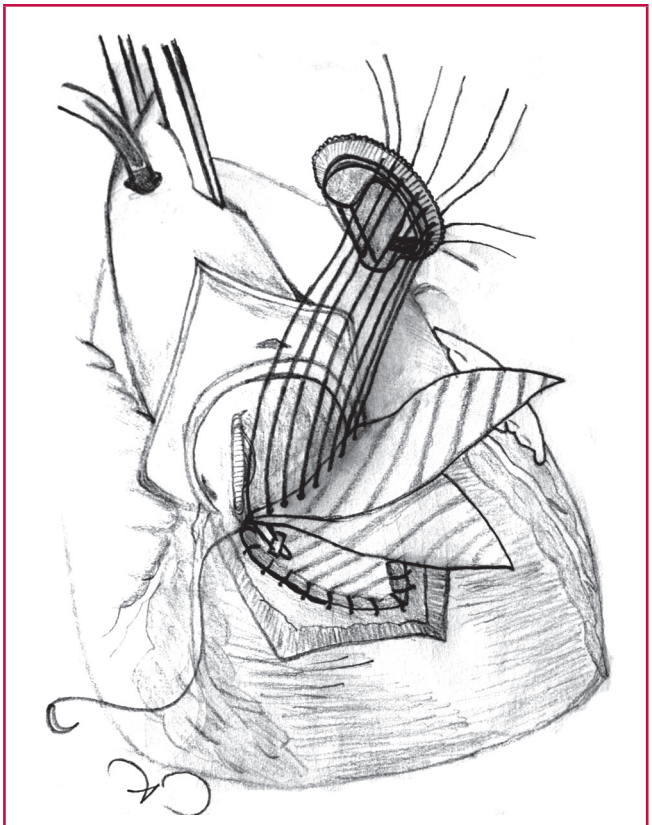

Fig. 2. The left ventricular outflow tract is reconstructed with two diamond-shaped patches. A no 23 St Jude prosthetic valve was implanted with interrupted stitches with Teflon felt.

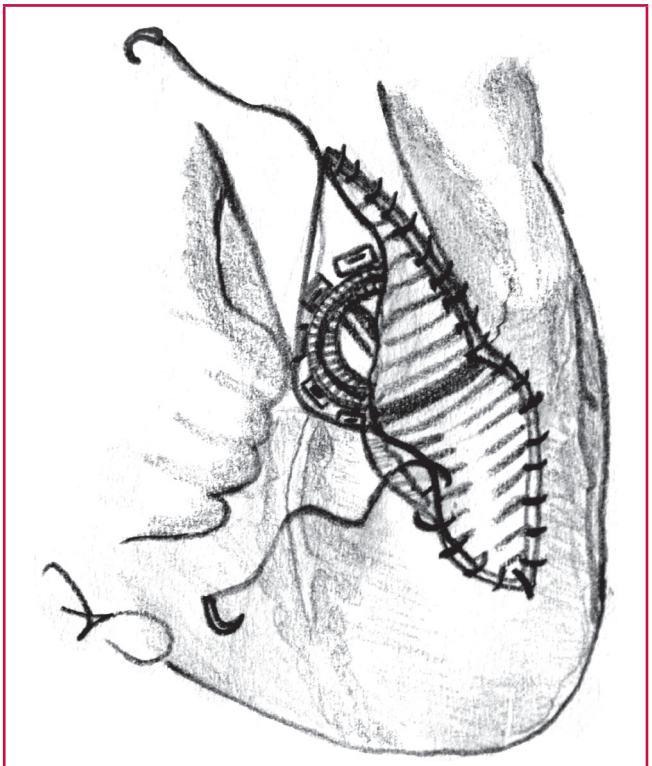

Fig. 3. The aorta and right ventricular outflow tract reconstructed with the patches.

In the late follow after five years, she was in NYHA class I. TEE revealed reduced interventricular septum thickness (12 mm), normal left ventricular function with a mean 10 mmHg and peak 20 mmHg gradients across the mechanical aortic valve. The peak gradient on the mechanical mitral valve was 6 mmHg. The right ventricle was normal with no regurgitation on the pulmonary valve.

Discussion

Aortoventriculoplasty, known as the Konno procedure, was first performed in October 1974 and was reported in 1975.[1] AVP is an established method of reconstruction of complex LVOT obstruction by the insertion of an adequately sized mechanical valve prosthesis after patch enlargement of the aortic annulus and septum. This method allows the implantation of a prosthetic valve, three or four sizes larger than the original size of the annulus.

It seems to be the most acceptable procedure in a patient with LVOT obstruction and concomitant MVR, since a mechanical mitral valve excludes the possibility of posterior annuloplasties such as the Nicks and Manouguian procedures.[5] We chose to perform aortoventriculoplasty because our patient had previously undergone AVR and MVR and echocardiography showed increased interventricular septum thickness with small aortic root.

Left ventricular function after AVP is important because the Konno procedure involves a longitudinal aortoseptal incision through a right ventricle incision.[6] The incision must be made parallel to the pulmonary artery ring. This incision could lead to maintenance of the left ventricular function and prevent

new-onset atrioventricular block.[4] The major morbidity after the Konno AVP is complete heart block. The incidence of pacemaker insertion following the Konno procedure has been reported to be from 6 to 12.5%.[2,7]

Another problem that may be encountered is dehiscence of the patch from the interventricular septum with communication between the left and right ventricles. This problem may require re-operation for correction of the ventricular septal defect. In addition, it is important to prevent damage to the first septal branch of the left anterior descending coronary artery.[8] There were no complications observed in our case.

Conclusion

Konno aortoventriculoplasty can be safely used in repeat AVR in adults, even if the patient has previously undergone a double valve replacement. This can be achieved with low operative mortality and good long-term outcome.

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Case Report

Late coronary stent dislodgement following coronary artery stenting

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Abstract

Recently, coronary artery stenting has been successful when used as an intervention for percutaneous coronary artery disease. However, the procedure may frequently produce complications. Although rare, stent dislodgement is one such complication, which may result in serious problems including coronary artery dissection, myocardial infarction, peripheral embolisation and death. Stent dislodgement is known to be an early complication of the coronary artery stenting procedure. In this case report, we present a 53-year-old male with late coronary stent dislodgement. To the best of our knowledge, no such case has been addressed in the literature to date.

Keywords: peripheral arteries, drug-eluting stent, complication, limb ischaemia, embolisation, coil/device, transcatheter, left main coronary disease

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In recent years, coronary artery stenting has been highly successful for the percutaneous treatment of coronary artery diseases.[1,2] As a result, once-rare complications have become more frequent.

Coronary stent dislodgement is one of these complications, which may result in occlusion or distal embolisation following peripheral or visceral drifting of the stent.[1,3,4] It may even lead to disruption of the coronary circulation, cardiac infarction, embolisation of the cerebrovascular system, peripheral embolisation and ultimately, death.[1]

Stent dislodgement has been reported in the literature as an early complication of the coronary artery stenting procedure. However, late coronary stent dislodgement has not been addressed to date.

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Case report

A 53-year-old male patient was admitted to our cardiology out-patient clinic with severe right groin pain. The medical history revealed hypertension, insulin-dependent diabetes mellitus and a previous coronary artery stenting procedure nine months earlier with a drug-eluting stent to the left main coronary artery (LMCA) and left anterior descending artery (Fig. 1).

The physical examination showed palpable femoral and distal arteries. There was no difference in the temperature or colour of both limbs. However, the patient had severe groin pain.

He was in normal sinus rhythm without a history of peripheral arterial disease. Coronary and peripheral angiographies were performed simultaneously through the contralateral femoral arteries. Coronary angiography revealed the LMCA stent was absent. Peripheral angiography revealed a right femoral artery flow defect with diminished distal flow (Fig. 2).

The patient was urgently operated on and a foreign body was detected within the artery and removed. It was stent material covered with tissue. The distal clamp was removed and the retrograde flow was good. A 4-F Fogarty catheter was directed to the distal and proximal artery to check the distal and proximal segments. No thrombus or other foreign body was found. The surgical procedure was successful.

After the procedure, the patient was symptom free and the distal arteries of the right lower limb were palpable. Repeated computed tomography showed that the LMCA had no significant lesion after distal embolisation of the stent. The stent in the left anterior descending artery was intact. The patient was discharged after four days.

Discussion

Today, coronary stenting is a widely used percutaneous intervention for the treatment of arterial diseases.[1,2] The use of drug-eluting stents (Sirolimus, Paclitaxel) has been significantly increased, due to their low potential for restenosis.[2]

Along with their benefits, however, drug-eluting stents may lead to complications, including challenges during deflation and removal of the balloon, endothelial dysfunction, vasospasm, hypersensitivity, infection, late malposition, late aneurysm formation, late restenosis, late stent fracture, late stent thrombosis, systemic and coronary embolisation and stent dislodgement.[2,5-7]

In our case, the patient had had a drug-eluting stent inserted, which had become dislodged. As shown by coronary angiography, the LMCA was too short and a drug-eluting stent was implanted on the discretion of the previous cardiologist. The stent appeared

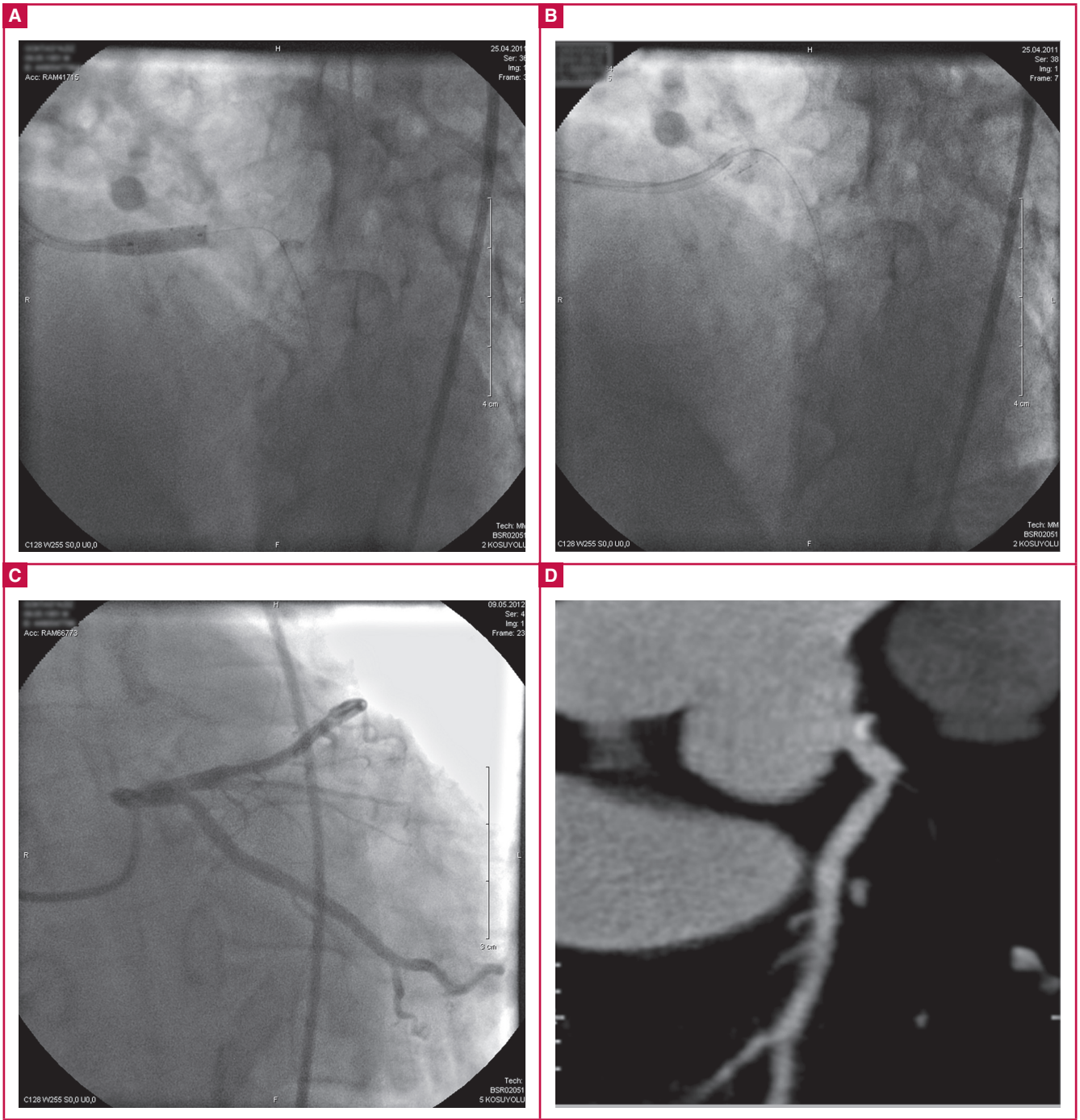

Fig. 1. A, B: Coronary angiography showing the stent implanted in the LMCA during baseline coronary angiography. C: Coronary angiography showing absence of the stent in repeated coronary angiographs. D: Computed tomography coronary angiography showing the absence of the LMCA stent.

to be protruding into the aorta due to the shortness of the LMCA. We therefore realised that the stent had migrated into the aorta over time and embolised in the femoral artery.

Studies have shown that the incidence of coronary stent dislodgement towards the peripheral or visceral arterial system ranges from 0.9 to 8.4%. Stent dislodgement usually occurs with previously inserted stents during retrieval of the stent–balloon complex into the catheter.[1,4] Along with this process, impaired guidance of the catheter or wire, tortuous vessels and severe calcification may contribute to dislodgement.[1,4]

Earlier studies have suggested that migration often occurs in the early period following coronary stenting. Siani *et al.*[3] reported a case of early coronary stent migration, where the migrated stent material was detected at the start of the right common femoral artery.[3] Another case report showed an early dislodgement of the coronary stent, in which the material was found in the right posterior tibial artery.[8] In a case report published by Castiglioni *et al.*,[9] the patient had recurrent angina pectoris after coronary stenting. The authors detected stent dislodgement into the ascending aorta.[9]

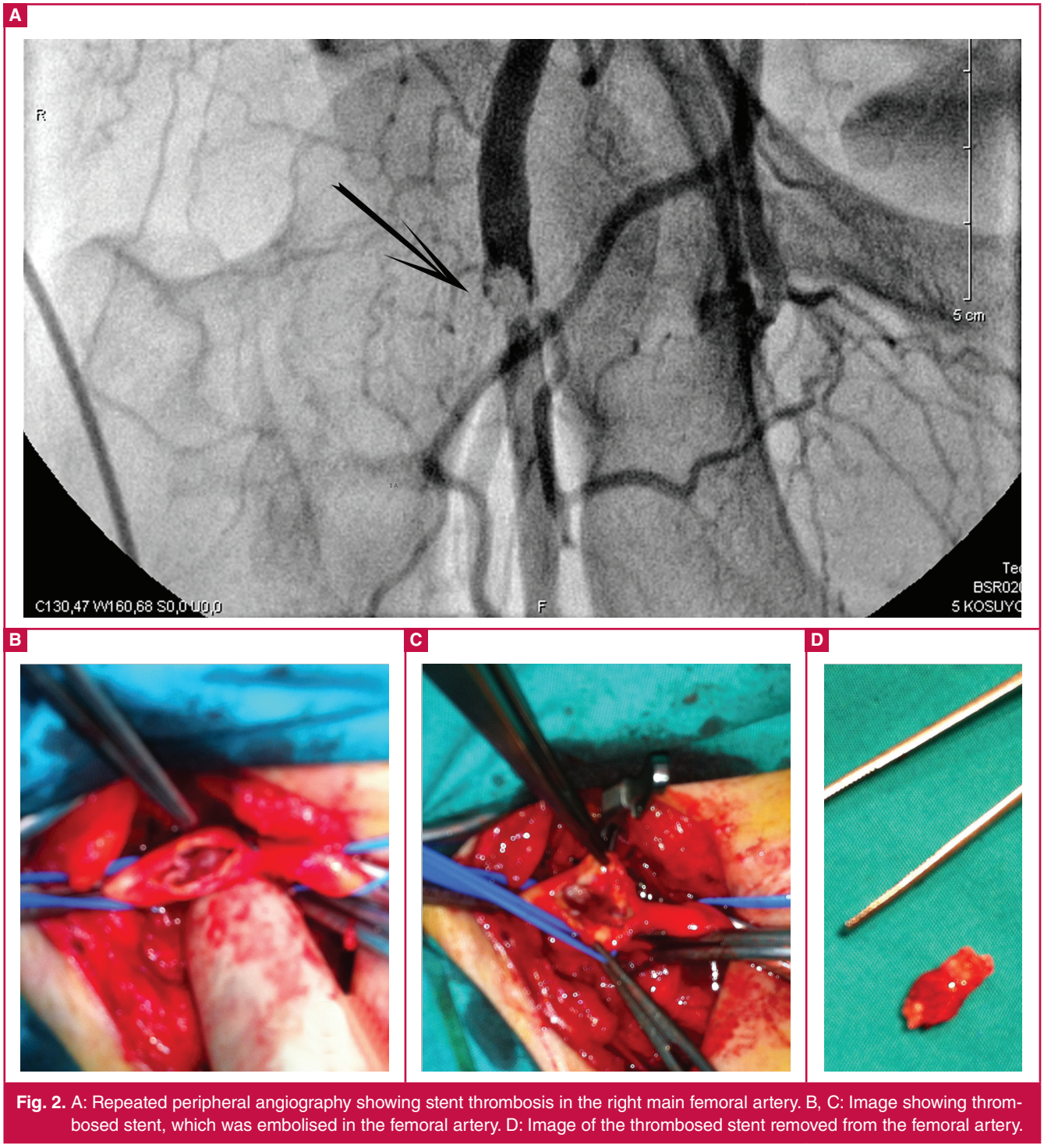

Fig. 2. A: Repeated peripheral angiography showing stent thrombosis in the right main femoral artery. B, C: Image showing thrombosed stent, which was embolised in the femoral artery. D: Image of the thrombosed stent removed from the femoral artery.

Late stent dislodgment has not been reported to date in the literature. In our case, the timing of this complication was interesting. Dislodgement had occurred nine months after the procedure and the proposal of late occurrence was supported by acute ischaemia and no history of peripheral arterial disease.

Conclusion

Coronary stent dislodgement is a rare complication of coronary artery stenting, which may result in acute peripheral artery occlusion and ischaemia. This complication may be seen both during early and late stages of the intervention. As a result, stent dislodgement should be considered in patients with acute peripheral arterial occlusion with a history of previous coronary stenting.

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Case Report

Treatment of an unusual complication of transfemoral TAVI with a new technique: successful occlusion of ventricular septal defect by opening the closure device in the ascending aorta

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Abstract

Ventricular septal defect (VSD) is a rare complication of transcatheter aortic valve implantation (TAVI) via the transfemoral approach. Aetiological factors leading to VSD have been reported as post-balloon dilatation, oversized prosthesis implantation, and severe calcification of the aorta. However, we present a case of VSD occurring after TAVI with an Edwards Sapien XT prosthesis without any distinct aetiological factors. We used a new technique for closure of the significant VSD; opening the left ventricular disc of the closure device in the ascending aorta and successfully implanting the device without any damage to the bioprosthetic valve.

Keywords: transcatheter aortic valve implantation, complication, ventricular septal defect

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Ventricular septal defect (VSD) is one of the rare complications of transfemoral transcatheter aortic valve implantation (TAVI).[1-2] In the literature there are four reported cases using the Edwards Sapien XT prosthesis (Edwards Lifesciences, Irving CA) and one case with a CoreValve ReValving system (Medtronic, Irvine, California).

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The most prominent aetiological factors for VSD formation are reported as post-balloon dilatation, oversized prosthesis implantation, and severe calcification of the aorta.[3-7] However, in this report, we present a VSD occurring after transfemoral implantation of an Edwards Sapien XT prosthesis, without any of these aetiological factors.

The VSD was successfully occluded retrogradely with a new technique. To our knowledge this report is the first describing successful closure of a VSD after TAVI with an Edwards Sapien XT prosthesis. We used a unique technique for the closure procedure.

Case report

A 73-year-old woman with dyspnoea in NYHA functional class III was referred to our institution for severe aortic stenosis. Transthoracic echocardiography (TTE) of the patient showed a calcific aortic valve with an area of 0.7 cm^2, and a mean gradient of 45 mmHg. The aortic annulus diameter measured by multislice computed tomography (CT) was 23 mm. There was no critical stenosis on coronary and peripheral angiography with a femoral artery diameter of 7 mm. Her logistic EuroSCORE was 33.8%.

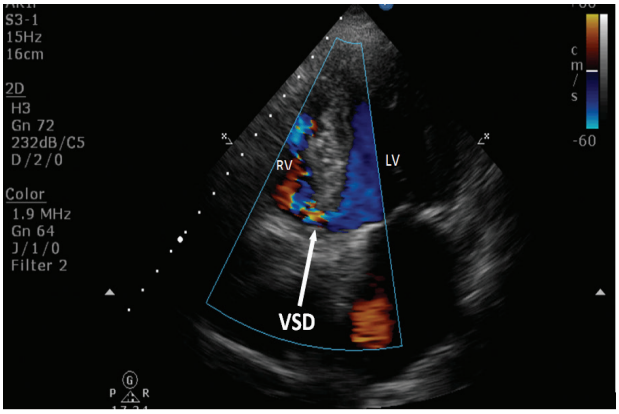

Fig. 1. Transthoracic apical four-chamber view showing left-to-right shunt at the interventricular septum level. VSD = ventricular septal defect; RV = right ventricle, LV = left ventricle.

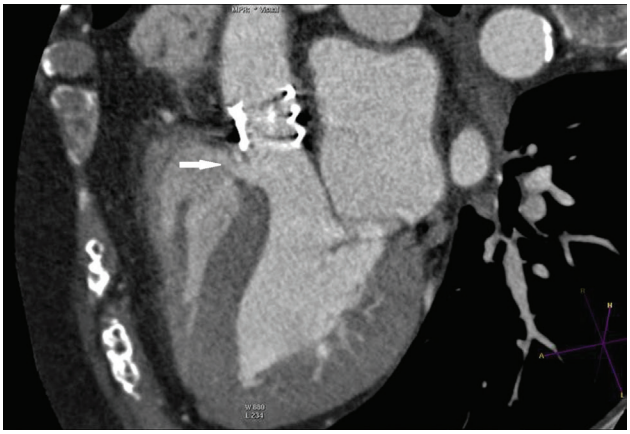

Fig. 2. Cardiac CT after transcatheter aortic valve implantation demonstrating ventricular septal defect (white arrow pointing at the defect).

A multidisciplinary decision was made to perform TAVI via the transfemoral approach. After aortic valve dilatation with a 23-mm balloon, a 26-mm Edwards Sapien XT prosthesis was successfully implanted.

The patient was asymptomatic post procedurally, however on her fourth day, control TTE showed prominent left-to-right systolic shunt at the membranous interventricular septum, with a Qp/Qs ratio of 1.5 (Fig. 1). Multislice CT demonstrated a free zone of septum about 3–4 mm from the prosthesis and a membranous type of VSD of 5 mm in diameter, which was not present before TAVI (Fig. 2).

With these findings, we decided to occlude the defect percutenously using an 8-mm muscular VSD occluder (AGA Medical Corp, MN, USA). However, with the close proximity of the defect to the prosthetic aortic valve, we risked valve dysfunction. We therefore prepared the cardiovascular team for emergency implantation of a new prosthetic aortic valve.

Under general anaesthesia the defect was crossed retrogradely (from prosthetic aortic valve to left ventricle and then right ventricle), and an arteriovenous loop was obtained. A 7-Fr TorqVue delivery sheath and dilatator (AGA Medical Corp, MN, USA) were advanced over the guide wire but we could not guide the delivery system towards the apex of the left ventricle.

We decided to open the left ventricular disc of the occluder in the ascending aorta and pull the disc through the prosthetic valve. Fortunately, the left ventricular disc passed through the prosthetic valve easily and was placed on the left ventricular wall. The prosthetic valve was still in the original place, and aortography showed no aortic regurgitation. Left ventricle angiography showed the size of the occluder was appropriate for the defect.

We then opened the right disc of the occluder. Following the release of the device, left ventricle angiography and complete transoesophageal echocardiography were performed and no residual shunting was observed. The aortic prosthesis was working well. The procedure was finished without any complications. Control multislice CT showed the VSD occluder with no residual shunt (Fig. 3).

After three days the patient was discharged home. The patient was symptom free at the nine-month follow up.

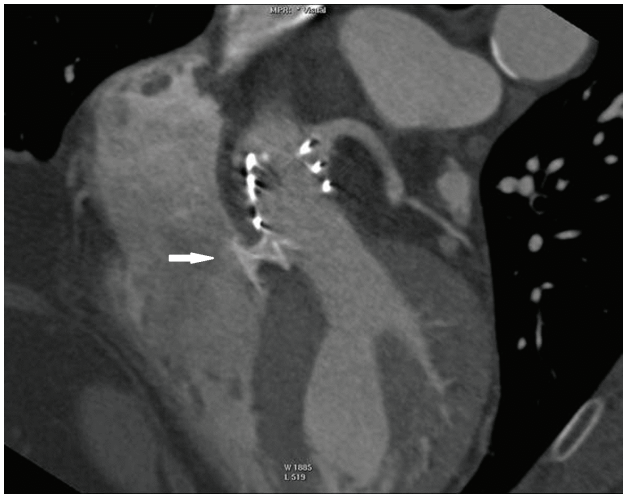

Fig. 3. Cardiac CT after occlusion of the ventricular septal defect (white arrow pointing at the occluder). There is no interference between the Amplatzer occluder and Edwards Sapien XT prosthesis.

Discussion

VSD is an unusual complication after transfemoral TAVI. In the literature there are only five reports (one in 2009 and the others in 2013) of VSD in five patients treated with the Edwards Sapien XT device and two patients with the CoreValve ReValving system.[3-7] In most of these cases, post-balloon dilatation of the device due to aortic regurgitation or oversized prosthesis implantation have been held responsible for this complication. In the remaining case there was no explanation other than excessive aortic calcification.

In our patient there was only mild calcification in the aortic root with a LVOT size of 23 mm detected by multislice CT before the procedure. A 26-mm Edwards Sapien XT device was implanted, and there was no need for post-procedural balloon dilatation. It was surprising to have a VSD complication in such a patient.

In our patient, although the defect was haemodynamically significant, she was asymptomatic, emphasising the importance of a careful echocardiographic evaluation post procedurally. Three of the VSD cases after TAVI (two with Edwards Sapien XT and one with CoreValve) reported in the literature needed no invasive treatment and were followed up medically. On the other hand, three patients (all with Edwards Sapien XT) had a surgical operation for the aortic valve and defect.[4-7] Percutaneous closure of the VSD after TAVI was reported for only one patient treated with the CoreValve ReValving system.[3]

This procedure has difficulties, such as properly advancing the delivery sheath into the left ventricle. We overcame this problem by opening the left ventricular disc in the ascending aorta and pulling it back through the prosthetic valve. There was, however, the risk of bioprosthetic aortic valve malposition and acute aortic regurgitation.

To our knowledge there is no such manoeuvre reported among the VSD cases with prosthetic aortic valves. We demonstrated that percutaneous treatment of the VSD after TAVI with an Edwards Sapien XT prosthesis could be performed without any complications.

Conclusion

VSD is a rare complication of TAVI and can occur without post-balloon dilatation, heavy calcification or oversizing of the valve. Although it is a serious problem, asymptomatic presentation may occur and routine careful TTE examination after TAVI is very important. Percutaneous treatment of this complication should not be thought of as a routine VSD occlusion procedure, and a cardiac team should be ready for implantation of a second valve. Opening of the occluder device in the ascending aorta may be done without any damage to the bioprosthetic aortic valve.

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Case Report

An unusual cause of generalised seizure following cardiac surgery: with bolus cefazolin administration

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Abstract

Although some of the aetiological factors of seizure, such as cerebral microemboli, cerebral oedema, hypoperfusion, cerebral hypoxia and metabolic encephalopathy cannot be completely controlled during cardiac surgery, cautious management of all steps in the procedure may prevent the administrative causes of seizure. Cefazolin, which is known to be a proconvulsant agent, may be a suspected agent of seizure complications in patients with renal insufficiency. Surprisingly, intravenous bolus administration of cefazolin may also trigger seizure in patients with normal renal function. In this case report, a complication of generalised seizure after cardiac surgery with intravenous bolus administration of cefazolin is described, along with a brief review of the literature.

Keywords: cardiac surgery, cefazolin, adverse effect, seizure

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Neurological complications are a major cause of morbidity and mortality during the immediate postoperative period following cardiac surgery. Although ischaemic stroke has the highest rate of incidence among neurological complications (range between 2 and 6% among patients who have undergone myocardial revascularisation), differing degrees of decrease in the level of consciousness, a more or less evident deterioration in neuropsychological function, and convulsive seizures may be observed during the immediate postoperative period following cardiac surgery.[1]

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The exact rate of incidence of seizures after cardiac surgery is not well studied and is reported in the literature as 0.5%.[2] Among the aetiological factors of seizures, cerebral microemboli (50%), cerebral oedema, hypoperfusion, cerebral hypoxia, metabolic encephalopathy (6–30%), and the effects of pharmacological agents used in anesthesia and during the peri- and postoperative periods have been considered.[1,2]

In this report, we present a case of generalised seizure in a coronary artery bypass surgery patient and analyse the aetiological factors in the context of the literature.

Case report

A 57-year-old, 83-kg, 176-cm male with a history of hypertension was admitted for coronary artery bypass surgery. Surgery was performed with the standard on-pump technique.

During extracorporeal circulation, his systolic blood pressure was maintained between 50 and 70 mmHg; haemoglobin and haematocrit levels were maintained above 8 g/dl and 27%, respectively. Intra-operative heparinisation was managed as standard procedure and the activated clotting time was maintained above 480 seconds.

There was no calcified plaque that could have caused embolism during surgery at the aortic cannulation and proximal bypass sites, and care was taken to avoid embolism of air, lipid and other particles. No extraneous blood was used during or after the operation.

Total surgery, cardiopulmonary bypass and cross-clamp times were 190, 76 and 43 minutes, respectively. Haemoglobin and haematocrit levels were 12 g/dl and 34%, respectively, after the operation.

Following an uneventful surgery, the patient was monitored in the intensive care unit (ICU). Around three hours after surgery, the patient was extubated without any surgical complication and was in a haemodynamically stable situation. However, he was observed by the ICU nurse to be 'shaking all over' during respiratory exercise 11 hours after the surgery, which was ameliorated through the management of anaesthesia. Sedation was achieved by the administration of propofol, and muscle relaxation was achieved with pancuronium bromide after the patient was intubated.

On further questioning, it was revealed that the patient had tonic stiffening followed by rhythmic myoclonic jerking and upward deviation of the head and eyes. A review of his medications revealed that the patient had received 1g of cefazolin 30 minutes before the skin incision (pre-operatively), 1 g of cefazolin three hours after the first administration (peri-

operatively) and 1 g of tranexamic acid (TA) peri-operatively, with the nurse reporting that 1 g of cefazolin was administered as an intravenous bolus injection about a minute before the seizure. Because of the sedation there were no lateralising postictal features.

Blood work revealed normal sodium, calcium and magnesium concentrations. The blood glucose level was 152 mg/dl (8.44 mmol/l), urea concentration was slightly elevated at 13.2 mmol/l, and creatinine was 164 mmol/l. The electroencephalogram was considered normal. Computerised axial tomography and magnetic resonance imaging scans of the head were performed and the results were normal. Electrolyte levels were within normal limits (sodium 142 mEq/l, potassium 4.3 mEq/l, chloride 104 mEq/l). Other neurological examinations were all within normal ranges.

The patient was treated with intravenous leviteracetam at a dose of 1 500 mg/day, administered in three doses over 30 min, after which he remained seizure free. The patient was easily extubated three hours later with no further neurological findings. He was monitored for one more day in the ICU and discharged to the general ward on postoperative day two.

The patient was discharged and allowed to go home after seven days with no further incidents of seizure. Leviteracetam was discontinued after seven days of treatment, and the patient has remained seizure free since discharge.

Discussion

Cardiac surgery may pose a significant threat to the nervous system via various mechanisms. Although the incidence of seizure is usually low, the causes and management are relatively unique in this setting.[2] Therefore the attending physician must be well versed in the most likely causes of seizure in this specific population, such that diagnosis and optimal management can be initiated rapidly without pursuing unnecessary and costly testing in all cases.

A targeted approach based on recognising focal versus generalised seizures, a careful review of the history and medications, and a focused approach will lead the clinician to choose the most effective therapy required. If the patient's history indicates a generalised seizure, the approach and differential are likely to be metabolic and/or toxic aetiologies. The usual suspects include deregulated electrolyte balance, such as hyponatraemia, hypo-/hyperglycaemia, hypocalcaemia, hypomagnesaemia, and, less commonly, hypophosphataemia.[1] In the case of the patient described here, no electrolyte or glucose imbalance was noted.

Renal dysfunction is one of the secondary reasons for seizure due to uraemia, which is known to lower the seizure threshold. Seizures may also arise from increased drug levels that may have proconvulsant effects. Specifically, these include penicillins, cephalosporins, imipenem (beta-lactam antibiotics) and fluoroquinolones.[2] In animal models, penicillin is commonly used to induce generalised epilepsy, characterised by generalised spike and wave discharges on an electroencephalogram.[2] Cefazolin, another beta-lactam antibiotic with similar proconvulsant activities, is the most potent gamma-amino-butyric acid (GABA) antagonist among the cephalosporins.[3]

Cefazolin has been reported to the United States FDA adverse-event reporting system 15 times between 2004 and 2012 for the induction of convulsions. In the present case, cefazolin was used as prophylactic antibiotic, 1 g pre-operatively, 1 g intra-operatively and a third dose was administered just a minute before the seizure in the intensive care unit.

Cefazolin, which is known to function as a proconvulsant in overdose, especially in patients with renal dysfunction, may lead to seizures because of malpractice by the nursing staff. The nurse's history in this particular case revealed that 1g of cefazolin was injected into the central venous port within five to seven seconds.

A detailed review of the history of all peri- and postoperative medication is helpful in elucidating the potential responsible agents. Unless absolutely necessary, no medication should be administered intravenously at a high rate.

Another important consideration is withdrawal reactions, for which the usual offenders are GABA agonists such as ethanol, benzodiazepenes and less commonly, baclofen and narcotics. These agents cause withdrawal reactions that may resemble seizure activity. This issue must be evaluated before surgery and may be the reason for convulsions.[3]

Tranexamic acid (TA), which is used as an antifibrinolytic agent during cardiac surgery, is another medication that has been shown to have proconvulsant activities *in vitro*.[4] In a study including a consecutive series of 1 188 patients receiving aprotinin or TA, 4.6% of the patients receiving TA were reported to have a seizure.[3] Manji *et al*. reported on a study sample consisting of 5 958 patients where the incidence of seizure was 7.4% among the patients receiving TA, compared to a seizure incidence of 0.94% in the controls.[4] The same authors also revealed a dose-dependent increase of seizure incidence in cardiac surgery patients.[4] When the TA dose was reduced, the seizure rate was concomitantly decreased.[4]

In the present case, only 1 g of TA was administered as an intravenous bolus after the patient was weaned from cardiopulmonary bypass. This dose (12.5 mg/kg) was very low when compared to the study reported by Manji *et al*.[4] As reported in the manufacturer's statement, the half-life of TA is three hours. Therefore the plasma concentration of TA may have been too low to have caused the seizure.

Finally, generalised seizures can be seen in the setting of multifocal injury, including so-called 'post-pump encephalopathy', which most likely represents multiple emboli of various particulate debris, including thromboemboli.[5] Watershed ischaemia from sudden hypotension can also result in symmetric cerebral injury, which has a typical magnetic resonance image appearance showing infarcts in the border zones between the major vascular territories. Watershed strokes are especially likely in the vasculopathic population in which carotid disease is likely to co-exist with coronary disease, such that relative hypotension is even less well tolerated.[5] In this case, cranial magnetic resonance imaging and computed tomography scans revealed totally normal findings.

Conclusion

Cardiac surgery may result in several complications during all courses of the procedure. A detailed review of the history of all peri- and postoperative medication is helpful in elucidating the possible responsible agent for generalised convulsion with no other aetiology. More importantly, it was concluded from this study that the administration of medication intravenously at a

high rate possesses a considerable risk and should only be done if absolutely necessary.

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Case Report

Takayasu arteritis in pregnancy

Priya Soma-Pillay, Adekunle Adeyemo, Farhana Ebrahim Suleman

Abstract

Takayasu arteritis is a chronic, granulomatous arteritis affecting large and medium-sized arteries. During pregnancy, maternal and foetal complications are largely as a consequence of maternal arterial hypertension. We present a case of a 35-year-old para one gravida two patient with Takayasu arteritis (group III disease) complicated by chronic hypertension and a severely dilated ascending aorta. Good blood pressure control during pregnancy is an important measure in reducing obstetric morbidity.

Keywords: Takayasu arteritis, pregnancy, hypertension, pre-eclampsia

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Takayasu arteritis is a chronic granulomatous arteritis affecting large and medium-sized arteries. The disease is characterised by inflammation of the blood vessels, resulting in destruction and distortion of the layered components of their walls. During the early stages of the disease, there are mononuclear cell infiltrations in the adventitia and granulomas with Langerhans cells in the media. This is followed by disruption of the elastin layer and subsequent massive medial and intimal fibrosis. These lesions result in segmental stenosis, occlusion, dilatation and aneurysmal formation in the affected vessels.[1]

Stenotic lesions predominate and have been reported in 90% of cases, while aneurysms are only reported in approximately 25%.[2] This is a disease of young adults with a peak onset in the second and third decades of life. A case series reported from South Africa of Takayasu arteritis in childhood demonstrated a 2:1 female-to-male ratio.[3] Patients with Takayasu arteritis may present with a variety of clinical manifestations, but arterial hypertension is the most common feature of the disease.[4]

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Case report

A 35-year-old para one gravida two patient, with a previous uncomplicated full-term delivery at the age of 16 years, was referred to the cardiac-obstetric unit at eight weeks' gestation. She had been diagnosed with Takayasu arteritis six years earlier, and tuberculosis two years previously, for which she was treated. She was hypertensive and her blood pressure was controlled with nifedipine, carvedilol and hydrochlorothiazide. The Takayasu disease was being treated with prednisone and azathioprine.

Further history revealed that her ascending aorta was dilated, and on evaluation by cardiothoracic surgeons, the lesion was considered to be inoperable. The patient was not using any contraception and this was a planned and wanted pregnancy. She had no other medical or surgical history of note.

On examination, the patient was apyrexial with a blood pressure of 120/70 mmHg in both arms and a pulse of 88 beats per minute. Cardiac examination revealed normal first and second heart sounds. No third or fourth heart sounds were heard and there was a one-quarter aortic regurgitation murmur. Respiratory and abdominal examinations were normal.

Ultrasound examination confirmed an intra-uterine pregnancy of eight weeks' gestation. The electrocardiogram was normal. On echocardiography, the patient had good left ventricular systolic function with no regional wall-motion abnormality. There was a tricuspid aortic valve with trivial aortic regurgitation. The ascending aorta was markedly dilated, measuring 5.7 cm. No dissection flap was seen.

The descending aorta and its branches had been evaluated by CT angiography two months prior to pregnancy. The ascending, arch and descending thoracic aorta were dilated (Fig. 1A, B) with marked mural thickening of the thoracic (2.3 cm) aorta (Fig. 2A, B). A laminated thrombus was found on the descending aorta. The renal arteries were patent. No abnormality was detected on fundoscopy.

Laboratory findings showed an elevated erythrocyte sedimentation rate of 56 mm/h and a C-reactive protein level of 9 mg/dl. The full blood count, renal function, electrolytes and urinalysis were normal.

The patient was managed by a multidisciplinary team of cardiologists, obstetricians and rheumatologists. After the initial investigations were performed, the patient was counselled about the aortic lesions. She was informed about the possibility of further dilatation or rupture of the aorta during pregnancy. The patient was offered a termination of pregnancy for medical reasons, which she declined.

The pregnancy was managed further by the multidisciplinary team and the patient was treated with prednisone (10 mg daily) and azathioprine (150 mg alternating with 200 mg daily) for Takayasu disease, methyl-dopa for hypertension, aspirin

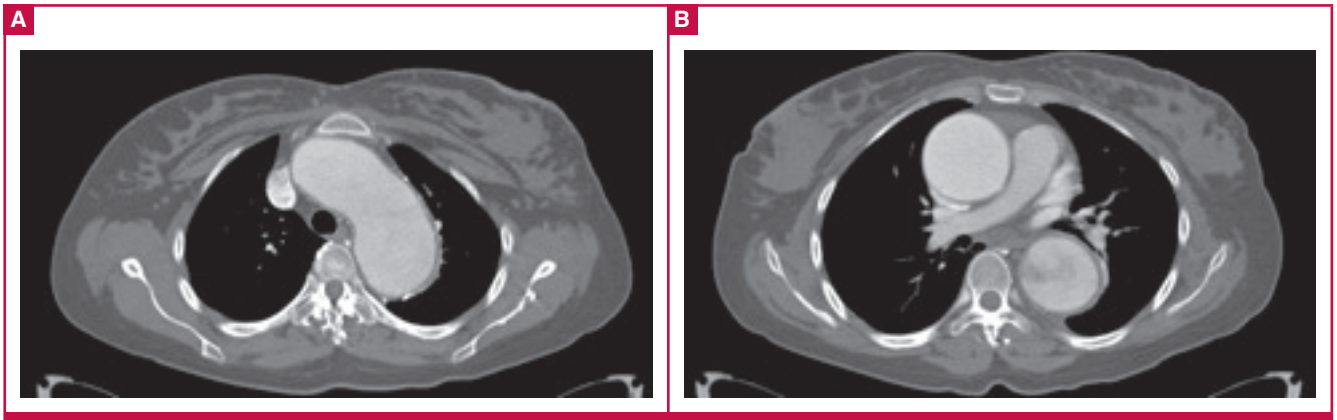

Fig. 1. Axial CT post-contrast images in the arterial phase demonstrating aneursymal dilatation of the arch of the aorta (A) and the ascending and descending aorta (B). Note the turbulent flow in the descending aorta.

and calcium gluconate for prevention of pre-eclampsia, and therapeutic enoxaparin for the thrombus in the descending aorta.

First-trimester foetal aneuploidy screening was negative and the foetus was also structurally normal. The patient was seen every two weeks at the cardiac-obstetric unit for evaluation of blood pressure, urinalysis and foetal growth. An echocardiogram was done monthly to evaluate the aorta for disease progression.

The antenatal course was uneventful. The blood pressure was well controlled (around 130/70 mmHg) with appropriate foetal growth. The patient was delivered by elective caesarean section with spinal anaesthesia at 34 weeks' gestation. A healthy baby weighing 2.3 kg with good Apgars was delivered. The mother was observed in a high-dependency unit for 24 hours after delivery where her blood pressure remained well controlled. After delivery, treatment with prednisone, azathioprine and enoxaparin was continued, methyl-dopa was stopped and nifedipine re-started and stool-softeners were also prescribed.

The patient was discharged five days after delivery. Repeat CT angiography and echocardiogram at the six-week postnatal visit was unchanged.

Discussion

Takayasu arteritis was first described in 1908 by the Japanese ophthalmologist who observed retinopathy in the absence of peripheral pulses. Autoimmunity, sex hormones (more common in females) and a genetic predisposition of the human leucocyte antigen have been proposed as possible causes.[5]

The disease is classified clinically into stages depending on the presence of complications such as hypertension, retinopathy, aneurysms and aortic insufficiency: group I, uncomplicated disease; group IIa, single complication with uncomplicated disease; group IIb, severe single complication with uncomplicated disease; group III, two or more complications with uncomplicated disease.[6] Our patient had group III disease.

Patients with Takayasu disease should be managed in a high-risk obstetric unit. Pregnancy is not associated with disease progression, however there is a 60% risk of complications developing during pregnancy.[7] Maternal risks are attributed mainly to arterial hypertension, and the most important risks include development of pre-eclampsia, exacerbation of chronic hypertension, heart failure, and cerebral vascular accidents.[8]

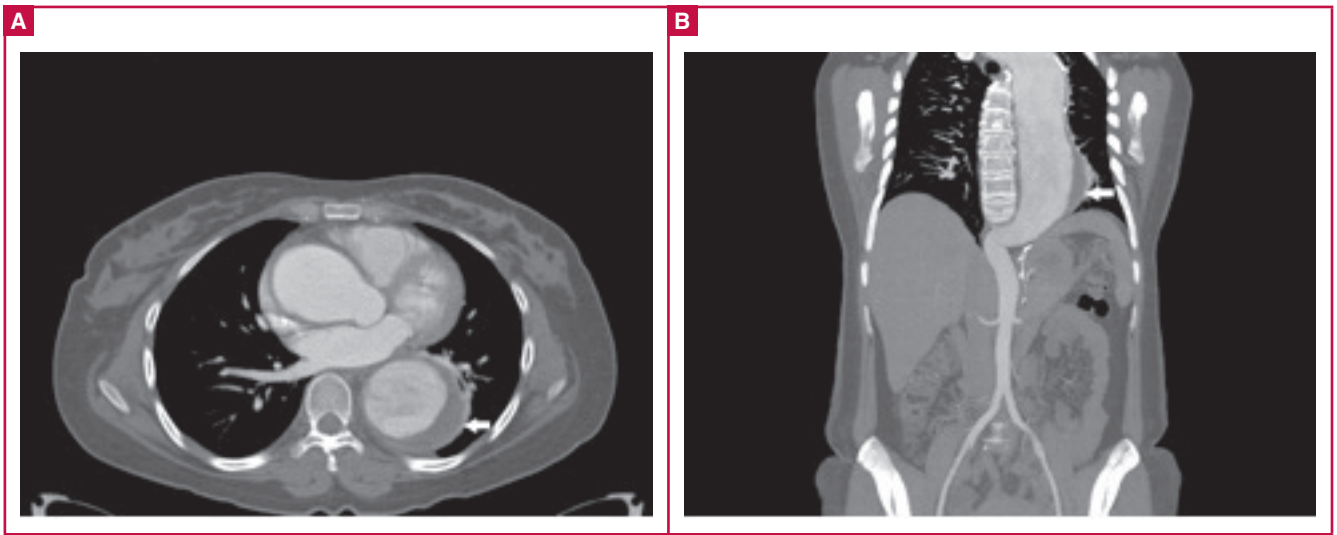

Fig. 2. Post-contrast CT images (A) in the axial post-contrast venous phase and (B) coronal curved reconstruction in the arterial phase demonstrating marked thickening of the wall of the thoracic aorta (arrows). Note the involvement of the thoracic aorta only, with sparing of the abdominal aorta.

Low-dose aspirin for pre-eclampsia prevention should be started before 16 weeks.

Lakhi and Jones reported a case of Takayasu arteritis complicated by aortic dissection in the peripartum period.[8] In this report, the patient's blood pressure remained elevated (160/91 mmHg) when she became symptomatic on the third postpartum day. In the 2003–2005 Confidential Enquiries into Maternal Deaths in the United Kingdom, aortic dissection was one of the leading causes of maternal death.[9] The deaths occurred mostly from failure to treat systolic hypertension.

Foetal complications such as growth restriction, miscarriage and foetal death have been reported in 60–90% of cases.[10] Foetal growth restriction is most likely the result of impaired placental blood flow caused by uncontrolled blood pressure and the involvement of the abdominal aorta and renal arteries. Another mechanism could be occlusion of the renal arteries, leading to an increase in renin production, with consequent increase in blood pressure.[11]

The mode of delivery is determined by the maternal haemodynamic status and by obstetric indications. Unfortunately there are very little data to guide clinicians as to the optimal mode of delivery. Labour and vaginal delivery with or without epidural anaesthesia is safe provided blood pressure is controlled.[8] Patients with Takayasu disease experience a severe elevation of systolic blood pressure during uterine contractions, compared to control patients, so regular monitoring of blood pressure is important during labour.[12] The second stage of labour should be shortened by the use of low forceps or vacuum delivery.

Leal *et al*. recommend vaginal delivery for patients in groups I and IIa, as long as epidural analgesia is used for pain relief and the second stage of labour shortened by vacuum or forceps.[5] Caesarean section is recommended for patients in group IIb and III because the increased blood volume and blood pressure observed during uterine contractions may lead to cardiac decompensation.[5] Regional anaesthesia has been reported successfully for caesarean delivery.[13] This method also allows monitoring of brain perfusion through the patient's level of consciousness. Our patient had an elective caesarean section because, although the blood pressure was controlled, her aorta was severely dilated. This put her at a significant risk of dissection or rupture of the aorta.

Patients should be nursed in a high-care unit postoperatively to allow for early detection of hypoperfusion of organs and hypertensive complications. After delivery, maternal peripheral resistance and left ventricular workload increases. This physiological change may lead to the development of pulmonary oedema, heart failure, renal dysfunction or cerebral haemorrhage.[14] Use of immunosuppressive treatment may also increase the risk of puerperal infection.

Conclusion

Patients with Takayasu disease in pregnancy are at risk of several obstetric complications. These patients should be jointly managed during pregnancy by obstetricians, rheumatologists and cardiologists. Systemic hypertension must be aggressively treated to reduce the risk of complications.

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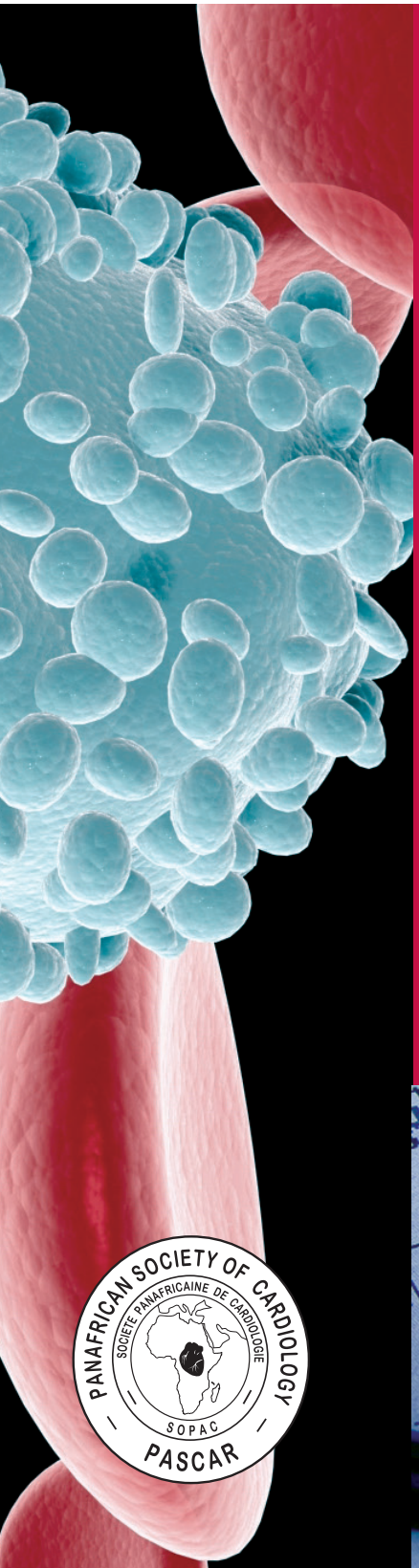

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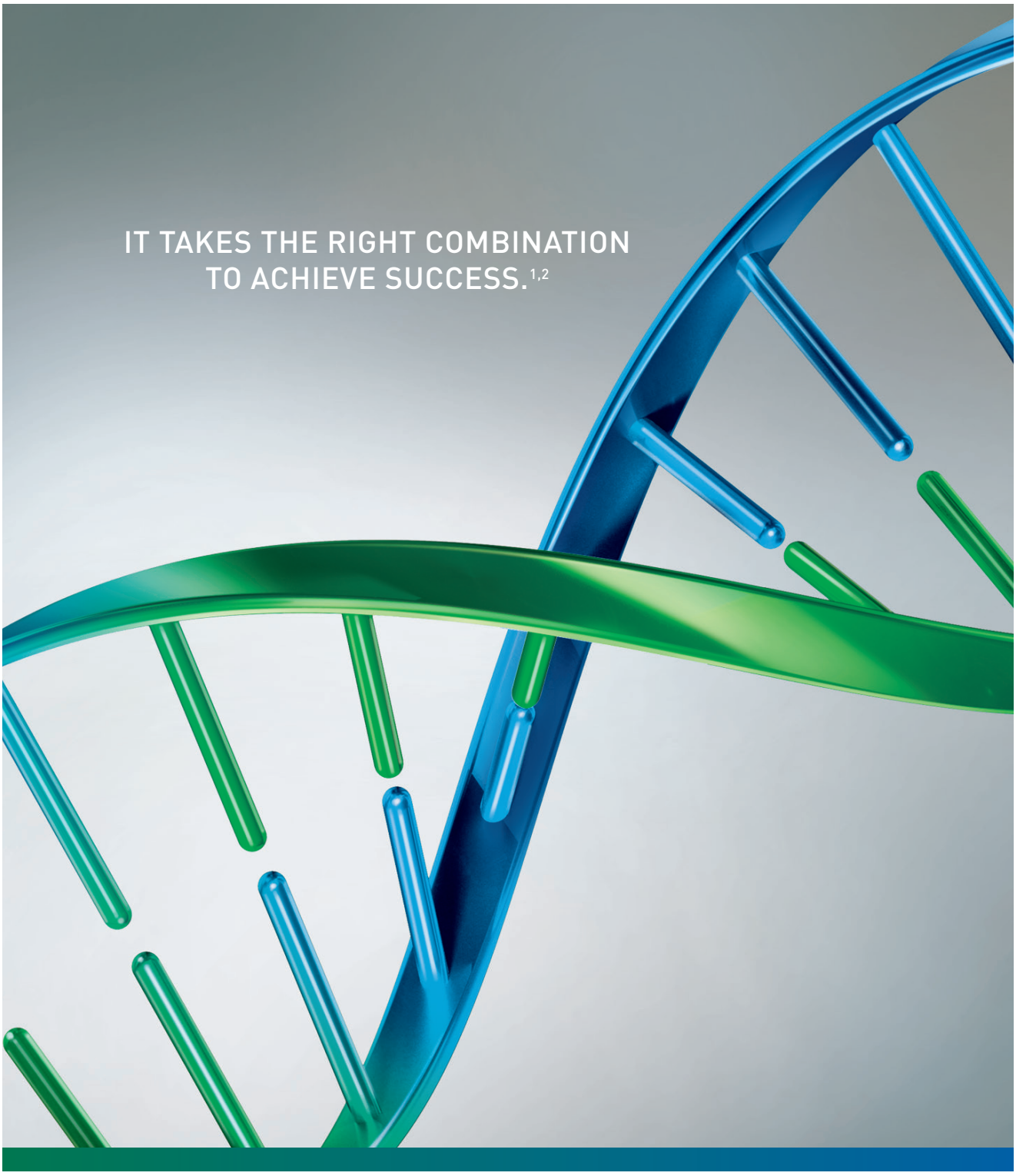

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