Cardiovascular Topics

Pulmonary hypertension as seen in a rural area in sub-Saharan Africa: high prevalence, late clinical presentation and a high short-term mortality rate during follow up

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Abstract

Introduction: The epidemiology of pulmonary hypertension (PH) in low- to middle-income countries is poorly characterised. We assessed the prevalence, baseline characteristics and mortality rate in patients with echocardiographically diagnosed PH at a rural cardiac centre in Cameroon.

Methods: We conducted a prospective cohort study in a subsample of 150 participants, aged 18 years and older, diagnosed with PH [defined as right ventricular systolic pressure (RVSP) ≥ 35 mmHg in the absence of pulmonary stenosis and right heart failure]. PH was classified as mild (RVSP: 35–50 mmHg), moderate (RVSP: 51–60 mmHg) and severe (RVSP: > 60 mmHg).

Results: Of 2 194 patients screened via echocardiograms, 343 (crude prevalence 15.6%) had PH. The sub-sample of 150 patients followed up (54.7% women, mean age of 62.7 ± 18.7 years) had a mean RVSP of 68.6 mmHg. They included 7.3% mild, 29.3% moderate and 63.4% severe PH cases. Co-morbidities included log smoke (80.7%), hypertension (52.0%), family history of cardiovascular disease (50.0%), diabetes (31.3%), alcohol abuse (21.3%) and HIV infection (8.7%). Main clinical features were dyspnoea (78.7%), fatigue (76.7%), palpitations (57.3%), cough (56.7%), jugular venous distension (68%) and peripheral oedema (66.7%). Overall, 70% presented in World Health Organisation functional class III/IV. PH due to left heart disease (PHLHD) was the commonest (64.7%), and rheumatic valvular disease accounted for 36.1%. The six-month mortality rate was 28%.

Conclusion: PH, dominated by PHLHD, was common among adults attending this rural centre and was associated with a high mortality rate. Related co-morbidities and late clinical presentation reflect the poor socio-economic context. Improved awareness of PH among physicians could promote early diagnosis and management.

Keywords: pulmonary hypertension, prevalence, mortality, Shisong, Cameroon

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Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) at or above 25 mmHg at rest.[1,2] It is currently classified by the World Health Organisation (WHO) into five subtypes, which include pulmonary arterial hypertension (PAH), PH due to left heart disease (PHLHD), PH due to lung disease or hypoxia (PHLDH), chronic thromboembolic PH (CTEPH) and PH due to unclear or multifactorial mechanisms (PHUM).[3,4]

The prevalence of pulmonary vascular disease in the developing world is unknown, but estimates suggest that about 25 million individuals may be affected.[5] Little information exists on the epidemiology of PH in sub-Saharan Africa, however there is some evidence that based on the high prevalence of risk factors such as rheumatic heart disease, schistosomiasis and HIV infection in this area of the world, the prevalence and mortality rate of PH may be higher than in Western countries.[6,7]

In South Africa, PH has been identified as one of the commonest causes of death, accounting for 31% of total cardiovascular deaths,[8] while only 8% of cardiovascular deaths in the United Kingdom were attributed to PH in 2012.[9] Furthermore, studies from the United States have shown that the prevalence of PH among African Americans is higher than in Caucasians.[10] These differences in the epidemiology of PH in different regions of the world are determined by genetic, geographic, environmental and socio-economic factors.

Left heart disease has been widely suggested to be the most common cause of PH. In developing countries, chronic infectious diseases, hypertensive heart diseases, cardiomyopathy and rheumatic heart disease are the main contributors.[6] This study aimed at determining the prevalence, baseline clinical characteristics and mortality rate during six months of follow up of patients with PH diagnosed via echocardiography at the rural Shisong Cardiac Centre (SCC) in Cameroon.

Methods

This was a prospective cohort study in a sub-sample of 150 participants aged 18 years and older who were diagnosed with PH via echocardiography. It was conducted at the Shisong Cardiac Centre from September 2013 to December 2014. This study also forms part of the Pan-African Pulmonary Hypertension Cohort study (PAPUCO).

Shisong is a rural village in the Kumbo sub-division of the north-west region of Cameroon. Shisong, on the outskirts of Kumbo town, is about 400 km north of Douala, the economic capital of Cameroon, and 450 km north-west of Yaoundé, the political capital of Cameroon.[11] The Shisong Cardiac Centre (SCC) is a well-equipped centre for the diagnosis and management of a variety of cardio-surgical conditions including PH. On average 185 echocardiographic examinations are done per month. In this study, the target population was restricted to patients living in rural or sub-urban areas, aged 18 years and above, who underwent echocardiographic examination at the centre between September 2013 and December 2014.

The PAPUCO study design and procedures have been described in detail elsewhere.[12] In brief, PH was diagnosed using echocardiography in patients with a right ventricular systolic pressure (RVSP) ≥ 35 mmHg in the absence of acute right heart failure (HF) and pulmonary stenosis. The data-collection form, adapted from the PAPUCO study, was used to obtain patients' information and clinical characteristics, including socio-demographic factors and past medical history [age, gender, body mass index (BMI), HIV status, family history of cardiovascular disease, systemic hypertension, dyslipidaemia, smoking and alcohol consumption], clinical presentation (dyspnoea, cough, fatigue, pedal oedema, palpitations and World Health Organisation functional classification).

At six months post-baseline, patients and/or their next-of-kin were contacted by phone to determine their vital status. For all fatal outcomes, the probable cause of death was assessed through a verbal autopsy.

Statistical analysis

Data were analysed using SPSS® (Statistical Package for Social Sciences for Windows) version 20. Qualitative variables are summarised as frequencies and percentages. Continuous variables are represented as means and standard deviations, or median (25th to 75th percentiles). Patients were categorised in three groups depending on PH severity; mild if RVSP was 36–50 mmHg, moderate if RVSP was 51– 60 mmHg and severe if RVSP was > 60 mmHg. We used χ^2 to compare proportions and Student's *t*-test or Kruskal–Wallis test to compare mean differences for continuous variables. Statistical significance was accepted at a *p*-value of 0.05.

Results

Out of a total of 2 194 patients who underwent cardiac echography at baseline, 343 had PH (prevalence rate 15.6%). Mean age was 61.9 ± 18.0 years and female gender (189, 55.1%) was predominant. As shown in Fig. 1, the peak prevalence of PH was noticed between 60 and 69 years (91/343, 26.5%).

Characteristics of the sub-sample followed up (n = 150) were similar to those of the overall PH group. The mean baseline age was 62.7 years [standard deviation (SD) =18.7]. Mean age did not

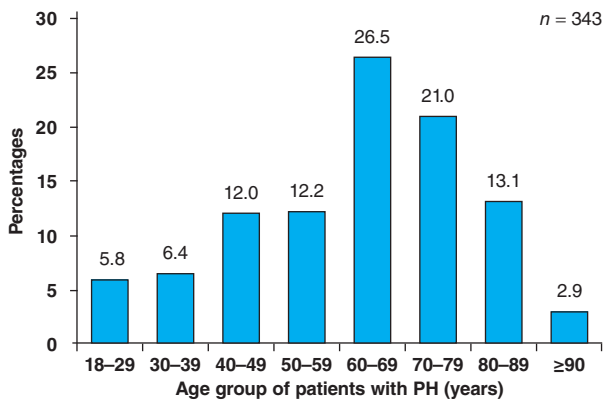


Fig. 1. Age distribution of patients with pulmonary hypertension in the Shisong Cardiac Centre.

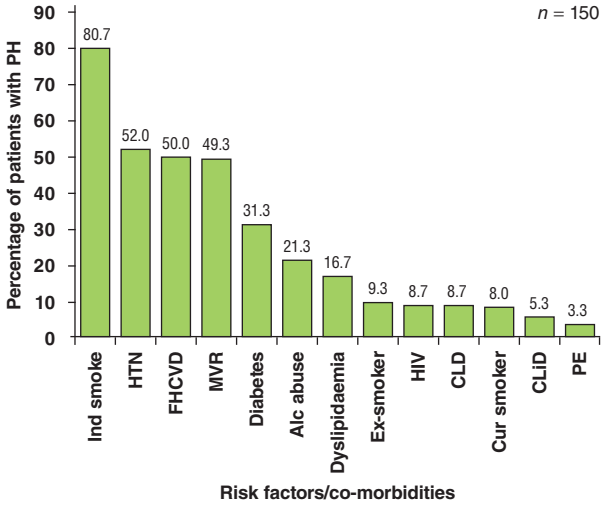
vary significantly by severity of PH ($p = 0.25$). Most participants (44.7%) had primary education, 32% had secondary education while 15.3% had never been to school. Variations by severity of PH were not significant ($p = 0.69$). The 150 followed-up participants included 11 (7.3%) with mild PH, 44 (29.3%) with moderate PH and 95 (63.4%) with severe PH. The proportion of women was 54.7% overall, and 5, 20 and 57%, respectively among the mild, moderate and severe PH groups ($p = 0.09$).

The distribution of risk factors for PH and co-morbidities are depicted in Fig. 2. Exposure to cooking fumes (80.7%), systemic hypertension (52.0%), family history of cardiovascular disease (50.0%), mitral valve regurgitation (49.3%), diabetes (31.3%) and alcohol abuse (21.3%) were the most common factors and co-morbidities identified in our study participants.

Dyspnoea (78.7%), fatigue (76.7%), palpitation (57.3%) and non-productive cough (56.7%) were the main symptoms reported by patients on initial presentation. Syncope (6.7%) and cyanosis (6.0%) were rarely reported by our patients. Most patients who participated in this study had distended jugular veins (68.0%) and peripheral oedema (66.7%). Table 1 summarises variations in clinical signs and symptoms with PH severity. Chest pain varied significantly with PH severity ($p = 0.03$)

Fig. 3 shows variations of the World Health Organisation functional class (WHO FC) according to PH severity. More than half (53%) of the patients presented in WHO FC III, 28% presented in class II, while 17 and 2% presented in class IV and I, respectively. Therefore a greater proportion of patients presented with marked functional limitation.

The main cause of PH was left heart disease (group 2), accounting for 64.7% of all cases, as shown in Fig. 4. In addition, 15.3% was due to unclear or multifactorial aetiology (group 5), 10% due to pulmonary arterial hypertension (group 1), 8% due to lung disease or hypoxia (group 3), and only 2% due to chronic thromboembolic mechanisms (group 4). Out of 97 participants with PHLHD, 50.5% had left ventricular systolic dysfunction (heart failure with reduced ejection fraction, HFrEF: EF ≤ 50%),



Ind Smoke = exposure to smoke from burning firewood, HTN = hypertension, FHCVD = family history of cardiovascular disease, MVR = mitral valve regurgitation, Alc abuse = alcohol abuse, CLD = chronic lung disease, Cur smoker = current smoker, CLiD = chronic liver disease, PE = pulmonary embolism.

Fig. 2. Risk factors and co-morbidities among 150 patients with pulmonary hypertension followed up at the Shisong Cardiac Centre.

Table 1. Clinical and echocardiographic findings of adult patients with PH

Parameters	*All* (n = *150*)	*Mild PH* (n = *11*)	*Moderate PH* (n = *44*)	*Severe PH* (n = *95*)	p-*value*
Clinical features at presentation					
Difficulty breathing (dyspnoea), *n* (%)	118 (78.7)	9 (7.6)	32 (27.1)	77 (65.3)	0.32
Cyanosis, *n* (%)	9 (6.0)	1 (11.1)	2 (22.2)	6 (66.7)	0.58
Non-productive cough, *n* (%)	85 (56.7)	10 (11.8)	22 (25.9)	53 (62.3)	0.14
Fatigue, *n* (%)	115 (76.7)	8 (7.0)	30 (26.0)	77 (67.0)	0.10
Syncope, *n* (%)	10 (6.7)	0	3 (30.0)	7 (70.0)	0.33
Palpitations, *n* (%)	86 (57.3)	8 (9.3)	28 (32.6)	50 (58.1)	0.06
Chest pain, *n* (%)	49 (32.7)	6 (12.2)	17 (34.7)	26 (53.1)	0.03
Distended jugular veins, *n* (%)	102 (68.0)	8 (7.8)	26 (25.5)	68 (66.7)	0.22
Peripheral oedema, *n* (%)	100 (66.7)	9 (9.0)	25 (25.0)	66 (66.0)	0.43
NYHA I and II, *n* (%)	45 (30.0)	3 (6.0)	19 (42.2)	23 (51.1)	0.13
NYHA III and IV, *n* (%)	105 (70.0)	8 (7.6)	25 (23.8)	72 (68.6)	0.13
Vital signs					
BMI (kg/m^2)	26.3 (18–46.8)	23.9 (21.2–26)	26.2 (18.6–42.4)	27.1 (18–46.8)	0.03
Systolic BP (mmHg)	126 (65–250)	133 (102–190)	123 (95–235)	127 (65–250)	0.26
Diastolic BP (mmHg)	79 (45–154)	73 (58–106)	78 (60–154)	80 (45–130)	0.73
Heart rate (beats/min)	88 (52–150)	96 (80–119)	88 (52–120)	86 (56–150)	0.43
Respiratory rate (breaths/min)	23 (13–40)	22 (19–28)	22 (13–35)	23 (15–40)	0.20
O_2 saturation (%)	93 (55–100)	90 (82–98)	94.5 (67–99)	91.5 (55–100)	0.37
Echographic parameters					
LVEDD (mm)	53 (16–72)	36 (18–56)	50 (38–70)	55 (16–72)	0.0001
LVESD (mm)	42 (13–60)	35 (13–43)	42 (22–60)	42 (18–97)	0.003
Ejection fraction (%)	48 (20–91)	66 (32–91)	46 (32–72)	46 (20–88)	0.06
Fractional shortening (%)	23 (6–95)	49 (28–61)	29 (18–33)	21 (6–95)	0.09
TAPSE (mm)	10 (7–25)	11 (8–20)	10 (8–17)	10 (7–25)	0.70

Data are number (%) or median (IQR).
BMI = body mass index, O_2 = oxygen, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, TAPSE = tricuspid annular plane systolic excursion.

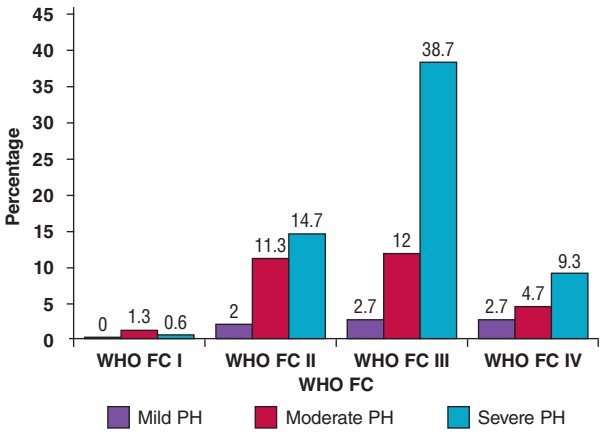


Fig. 3. Distribution of patients across WHO functional classes and PH severity.

36.1% had valvular heart disease and 13.4% had left ventricular diastolic dysfunction (HFpEF: EF > 50%).

The duration of follow up of the 150 participants ranged from five to 180 days. After a median follow up of 90.5 days, 42 deaths (cumulative mortality rate of 28%) were recorded. Equivalent figures were five deaths (cumulative incidence 45.5%) in mild PH, nine deaths (cumulative incidence 20.5%) in moderate PH and 28 deaths (cumulative incidence 29.5%) in severe PH ($p = 0.28$).

Discussion

Our study aimed at determining the prevalence, clinical profile and mortality rate from PH in a rural setting in sub-Saharan Africa. We noted a high prevalence of PH, late presentation to healthcare facilities in an advanced state of heart failure, and consequently a high mortality rate at six months of follow up. These findings could be attributed to the poor socio-economic status, hyper-endemicity of risk factors for PH, and limited availability of PH-specific drug therapies. In the PAPUCO study,[7] which was a multinational study on the epidemiology of PH in Africa with recruitment centres mostly in urban areas, similar findings were noted. Therefore it can be said that PH still presents a challenge on the African continent overall and not only in the rural setting.

Our observed prevalence of 15.6% is higher than the average of 10% prevalence observed in Australia in 2012 and

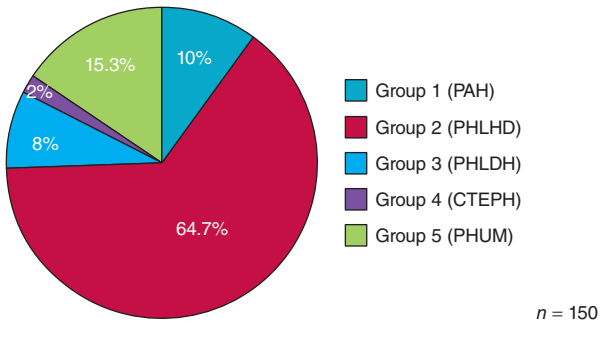


Fig. 4. Patient distribution according to the updated clinical classification of PH.

in other European countries.[13] This is somewhat to be expected considering the high burden of risk factors such as rheumatic heart disease, schistosomiasis, tuberculosis, sickle cell disease and HIV infection in sub-Saharan Africa, in addition to other risk factors shared with high-income countries. In addition, the SCC is located in a rural area that is difficult to access. Therefore, patients are usually reluctant to visit the centre until they are in advanced disease states or when referred by cardiologists. A recent expert review on the global perspective of the epidemiology of PH also supports our findings.[6] Among the several co-morbidities assessed in our study population, exposure to cooking fumes was the most common, especially in women. This most likely results from the common practice in Africa and Cameroon, particularly in the rural setting, where women cook using open fires, unlike in high-income countries. Systemic arterial hypertension was also common and in line with studies from Africa,[7] USA[14,15] and Germany.[16]

Hypertension is very common in sub-Saharan Africa where it affects about 30% of the adult population, and mostly goes undetected, undertreated and inadequately controlled.[17] It is the principal cause of HF in sub-Saharan Africa. In the Pan-African THESUS-HF registry of HF for instance, it was estimated that up to 50% of HF cases were due to uncontrolled hypertension.[18]This high prevalence of uncontrolled hypertension would most likely also account for the high proportion of PHLHD in our study population. With the growing epidemic of HF, LHD is now globally recognised as the main cause of PH.[6,7,13] PHLHD was dominated by patients with left ventricular systolic dysfunction, while PH due to rheumatic valvular heart disease is still common in our setting.

The clinical presentation was dominated by exertion dyspnoea, fatigue, cough and palpitations, which are common and non-specific symptoms in most patients with cardiovascular and/or respiratory conditions. Study participants were slightly overweight with a mean BMI higher than observed in a study in Nigeria,[19] but lower than reported in the USA.[15] Most of our participants presented with moderate to severe functional limitation, with 70% of them presenting in WHO FC or New York Heart Association (NYHA) class III and IV.

These findings are similar to those in the PAPUCO study,[7] and to those of Baptista and colleagues in Portugal in 2013,[20] who observed that 71% of their patients presented in WHO FC III and IV, as well as those of Fikret and colleagues in Germany.[16] This global observation of late presentation to medical attention could be explained by the fact that most symptoms and signs of PH are non-specific and therefore cases are usually misdiagnosed in primary care until the later stages when patients seek specialist care. Furthermore, in Africa, poor access to healthcare, limited availability of diagnostic tools for PH, and the general reluctance of patients in rural settings to seek medical attention until the later stages of illness could explain at least in part the late presentation.

About a third of our patients died within the first six months of being diagnosed with PH. This mortality rate is three times higher than that observed in the USA[15] and the UK.[9] The high mortality rate in our setting is most likely accounted for to some extent by the unavailability of disease-specific drug therapies. The fact that patients present at an advanced stage of the disease, and their inability to comply with follow-up visits reflects to some extent their limited financial coping capacity, resulting in death in the absence of adequate care.

Limitations

Our study has some limitations. Some cases of PH could have been missed because indications for cardiac echocardiography are usually symptom driven. This would lead to over-diagnosis of patients with severe disease, and accordingly, poor outcomes. Therefore whether our finding reflects those of a typical population with PH in this setting is unknown. Diagnosis of PH in our study was done by echocardiography, which is more a screening tool for PH, while right heart catheterisation (RHC), which is the gold standard for diagnosing PH, was not used. Therefore, cases of mild PH could have been missed in our study. Furthermore the operator-dependent nature of echocardiography could lead to over- or under-diagnosis. Despite the fact that echocardiography is only a screening tool, it is paramount in the diagnosis of PH as it is non-invasive, more available and less expensive compared to RHC. Moreover, in expert hands, it yields reliable and reproducible results. Indeed, studies carried out to evaluate the diagnostic accuracy of echocardiography compared to RHC have demonstrated a sensitivity of 83% and a specificity of 72%.[21]

Conclusion

Our findings suggest that PH is very common among patients attending our rural cardiac centre, with PHLHD being the most frequent type, and the short- to medium-term mortality rate being excessively high. Patients tend to present in advanced stages of disease and usually with several co-morbidities, most of which are cardiovascular conditions. Healthcare practitioners in this setting should be made more aware of this devastating condition, in order to prompt timely referral to specialised centres for proper evaluation and care of patients with suspected PH.

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Does the use of N-butyl-2 cyanoacrylate in the treatment of lower extremity superficial varicose veins cause acute systemic inflammation and allergic reactions?

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Abstract

Introduction: In this study we used N-butyl-2 cyanoacrylate (NBCA), including dimethyl sulfoxide (DMSO), via the endovenous route, for mechanochemical ablation in the treatment of superficial venous insufficiency, in an attempt to establish whether an early systemic inflammatory response and an allergic reaction occurred in the patients.

Methods: A total of 102 patients were treated with endovenous medical ablation in two centres between October 2015 and February 2016. This study was a two-centre, retrospective, non-randomised investigational study. Ablation treatment with endovenous NBCA was used in patients with C3 to C4b grade superficial venous insufficiency, according to the CEAP (clinical, aetiology, anatomy and pathophysiology) clinical classification, with sapheno-femoral junctional insufficiency and a reflux of 0.5 seconds and longer on duplex ultrasonography. Pre-operative whole blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level and blood chemistry were studied in all patients on admission to the clinic, and repeated in the second hour post-intervention.

Results: All patients were treated successfully. Pre-operative white blood cell count (WBC) was $6.82 \pm 1.67 \times 10^9$ cells/µl, and post intervention it was $6.57 \pm 1.49 \times 10^9$ cells/µl; the difference was not statistically significant ($p = 0.68$). The neutrophil count before the intervention was $4.09 \pm 1.33 \times 10^9$ cells/µl, while afterwards, it was $4.09 \pm 1.33 \times 10^9$ cells/µl, with no statistically significant difference ($p = 0.833$). Pre-intervention eosinophil count was $0.64 \pm 1.51 \times 10^9$ cells/µl, while it was $0.76 \pm 1.65 \times 10^9$ cells/µl after the intervention, and the difference was statistically significant. Pre-intervention ESR and CRP values were 18.92 ± 9.77 mm/h and 1.71 ± 1.54 mg/dl, respectively. Postoperative ESR and CRP values were 19.78 ± 15.90 mm/h and 1.73 ± 1.59 mg/dl, respectively, but the differences were not statistically significant. When the parameters were analysed by gender, the differences between pre- and postoperative WBC and eosinophil count, ESR and CRP in women were not statistically significant. On the other hand, although the change in WBC count and CRP value were not statistically significant in males, the differences in eosinophil count and ESR were statistically significant.

Conclusion: Cyanoacrylate has been used in the endovenous medical ablation of varicose veins and superficial venous insufficiency over the last few years without the use of thermal energy and tumescent anaesthesia, which represents the greatest advantage of this method. In addition, since it causes no systemic allergic or acute inflammatory reaction, it appears to be safe to use.

Keywords: N-butyl-2 cyanoacrylate, lower-extremity superficial varicous vein, acute systemic inflammation, allergic reaction

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Lower extremity venous insufficiency and the secondary development of varicose veins are important health problems that are frequently encountered in society. They impair the quality of life of individuals, and in certain conditions cause severe complications. The prevalence of venous insufficiency has been reported to be between 20 and 40% in many studies.[1,2]

Surgery has been the preferred method of treatment for this disease for more than 100 years. However, due to postoperative complications and frequent recurrence, alternative methods of treatment have been sought. Newly developed endovascular techniques have gradually replaced open surgery during the last two decades.

Haematoma, paresthesia, wound site scars, deformities, and a high rate of recurrence are among the complications of surgery.[3,4] Minimally invasive endovenous thermo-ablation techniques (radiofrequency and laser), applied in the last decade in the treatment of superficial venous insufficiency and varicose veins, have decreased postoperative complications, shortened the healing process and improved quality of life.[5] However, the necessity of tumescent anaesthesia during these techniques, and complications in the postoperative period, such as pain, ecchymosis and paresthesia caused by perforation of the vein wall, have limited the use of these techniques.[6,7]

The introduction of cyanoacrylate (CA) in medical applications dates back to the 1960s. Surgeons used CA in order to stop bleeding and close wounds during the Vietnam War.[8] Also, endoscopic CA injection to stop gastric variceal bleeding has been safely and widely used.[9] Recently, it has been used in the closure of type I and II endoleaks developing during the repair

of abdominal aortic aneurysms, varicoceles, pelvic congestion syndromes and arteriovenous malformations.[10]

N-butyl-2 cyanoacrylate (NBCA) has been used via the endovenous route in the treatment of venous insufficiency and varicose veins, with the aim of biochemical ablation.[11] NBCA rapidly hardens in a polymerisation reaction following intravenous injection and occludes the vein. In addition, it causes a local inflammatory reaction in the vein wall and surrounding tissues.[10,12] However, there are no studies in the literature evaluating whether NBCA causes systemic inflammation following contact with the blood circulation.

We attempted to establish whether NBCA caused a simultaneous systemic inflammatory response in the early period while causing a local inflammatory reaction in the vein wall and surrounding tissues in patients who were administered NBCA, including dimethyl sulfoxide (DMSO), for the treatment of superficial venous insufficiency. We retrospectively evaluated pre- and post-interventional blood samples in order to determine this.

Methods

This study was a two-centre, retrospective, non-randomised investigational study. Ablation treatment with endovenous NBCA was applied to patients with C3 to C4b grade venous insufficiency, according to the CEAP (clinical, aetiology, anatomy and pathophysiology) clinical classification, with sapheno-femoral junctional insufficiency and a reflux of 0.5 seconds and longer on duplex ultrasonography, between October 2015 and February 2016. This treatment was abandoned in patients with a greater saphenous vein diameter of > 15 mm and < 5 mm.

The treatment is contra-indicated in patients who have a past history of deep venous thrombosis, have femoral vein insufficiency, congenital vasculopathy, thrombophilia, the presence of severe systemic disease, and in pregnant and lactating patients. This procedure was not used in any patient who had any of these conditions.

Detailed demographic data of the patients who were treated using endovenous NBCA ablation therapy were collected. Whole blood count, sedimentation rate, C-reactive protein (CRP) and blood chemistry were studied in all patients on admission to the clinic. These examinations were repeated in the second hour post-intervention.

Patients who were taken into the operating room to undergo endovascular medical ablation were monitored by the anaesthesiology team. Subsequently, both legs were re-evaluated with Doppler ultrasonography. The integrity of the iliac vein and inferior vena cava in the abdominal region was confirmed in order not to overlook some rare conditions, such as possible inferior vena cava agenesis.

Patients were placed in the supine position and the leg and inguinal region were cleaned and draped in order to perform the intervention under sterile conditions. With the aid of Doppler ultrasonography, an appropriate segment of the greater saphenous vein was selected for catheterisation, and a 5F introducer sheath was placed following local anaesthesia. The placement of the catheter was confirmed by ultrasonography.

A 0.035-inch J guidewire was advanced into the sheath. Ultrasonography was used to determine whether the guidewire had reached the sapheno-femoral junction and a 4F carrier catheter was advanced into it. The catheter was confirmed to be at the sapheno-femoral junction and then withdrawn 3 mm, and a 3-ml syringe and piston system, which provides NBCA injection, was positioned. The location of the catheter was checked again by ultrasonography and it was confirmed not to be in the sapheno-femoral junction. The junction was then compressed by the ultrasonography probe and obstructed

The piston of the syringe administered 0.3 ml of NBCA during each pulse into the saphenous vein and compression was performed simultaneously. Intravenous administration of NCBA, which provided medical ablation, was continued while the catheter was withdrawn rapidly at a rate of 2 cm/s. At the end of the procedure, compression was continued for five to 10 seconds and the procedure was terminated after the sapheno-femoral junction was demonstrated by ultrasonography to be open and the rest of the greater saphenous vein was occluded.

A compression sock was placed on the leg that underwent the procedure and medium pressure was applied. The patient was taken to the ward for follow up and repeat testing of the whole blood count, blood chemistry, CRP and sedimentation rate. Patients with no complications in the eighth hour postoperatively were discharged with a follow-up plan of visits on the 10th day, and one, three, six and 12 months postoperatively.

Statistical analysis

The results were evaluated using SPSS version 17. Changes in the patients' values were calculated using the paired-samples *t*-test. The α-value was accepted as 0.05. The change in values by gender was calculated using the independent-samples *t*-test ($p < \alpha$ was accepted as significant).

Results

A total of 102 patients were treated with endovenous medical ablation at two centres between October 2015 and February 2016. The mean age of the patients was 51.16 ± 1.17 years (range: 25–74); 72 (70.6%) were female and 30 (29.4%) were male. The mean diameter of the saphenous vein was 7.72 ± 2.02 mm (range: 6–14). Among the general risk factors, a positive family history was present in 31 cases (30.3%), use of tobacco products in 17 (16.7%), hypertension in six (5.9%), abnormal lipid profile in 19 (18.7%), obesity in 24 (23.5%) and diabetes mellitus in five cases (4.9%) (Table 1).

Table 1. Demographics of the patients

Demographic data	*Number (%)*
Age (years)	51.16 ± 1.17
Gender (female/male)	72 (70.6)/30 (29.4)
Presence of family history	31 (30.3)
Use of tobacco products	17 (16.7)
Hypertension	6 (5.9)
Abnormal lipid profile	19 (18.7)
Obesity (BMI ≥ 30 kg/m^2)	24 (23.5)
Diabetes mellitus	5 (4.9)
CEAP classification	
C3	42 (41.2)
C4a	37 (36.3)
C4b	23 (22.5)
Vein diameter (mm)	7.72 ± 2.02

BMI: body mass index; CEAP: clinical, aetiology, anatomy and pathophysiology.

Table 2. Pre- and postoperative changes in whole blood and serological parameters of patients

Parameter	*Pre-operative value*	*Postoperative value*	*Amount of change*	t-*value*	p-*value*
WBC (× 10^3 cells/µl)	6.82 ± 1.67	6.57 ± 1.49	0.24 ± 1.33	1.846	0.068
Neutrophils (× 10^3 cells/µl)	4.09 ± 1.33	4.09 ± 1.33	–0.00 ± 0.02	0.211	0.833
Eosinophils (× 10^3 cells/µl)	0.64 ± 1.51	0.76 ± 1.65	–0.11 ± 0.46	–2.624	0.010*
Basophils (× 10^3 cells/µl)	0.14 ± 0.43	0.06 ± 0.13	0.08 ± 0.42	1.966	0.052
Haemoglobin (g/dl)	13.79 ± 1.47	13.84 ± 1.61	–0.05 ± 0.80	–0.503	0.617
Haematocrit (%)	42.00 ± 3.82	42.54 ± 7.11	–0.53 ± 5.78	–0.656	0.515
Platelets (× 10^3 cells/µl)	238.01 ± 64.33	225.40 ± 78.97	12.61 ± 75.39	1.285	0.204
Sedimentation (mm/h)	18.92 ± 9.77	19.78 ± 15.90	–0.86 ± 12.29	–0.709	0.480
CRP (mg/dl)	1.71 ± 1.54	1.73 ± 1.59	–0.21 ± 0.59	–0.634	0.714
Rheumatoid factor (IU/ml)	6.89 ± 5.52	6.65 ± 4.92	0.23 ± 3.80	0.634	0.527

WBC: white blood cells; CRP: C-reactive protein. *$p < 0.05$ statistically significant.

When the distribution of CEAP classification was analysed, 42 (41.2%) patients were found to be C3 grade, 37 (36.3%) were C4a, and 23 (22.5%) were C4b. All patients were treated successfully. Pre-operative white blood cell count (WBC) was 6.82 ± 1.67× 10^9 cells/µl, while after the intervention it was 6.57 ± 1.49 × 10^9 cells/µl; the difference was not statistically significant ($p = 0.68$). The neutrophil count before the intervention was 4.09 ± 1.33 × 10^9 cells/µl, and post intervention it was 4.09 ± 1.33× 10^9 cells/µl, with no statistically significant difference ($p = 0.833$). The eosinophil count was 0.64 ± 1.51 × 10^9 cells/µl prior to the procedure, and after the procedure it was 0.76 ± 1.65 × 10^9 cells/µl. The difference was statistically significant, demonstrating a negative correlation ($p = 0.01$) (Table 2).

Pre-intervention sedimentation rate and CRP values were 18.92 ± 9.77 mm/h and 1.71 ± 1.54 mg/dl, respectively, and postoperative values were 19.78 ± 15.90 mm/h and 1.73 ± 1.59 mg/dl, respectively. The differences were not statistically significant ($p_{sedim} = 0.480$, $p_{CRP} = 0.714$). The change in values pre- and post intervention are presented in detail in Table 2.

The change in values by gender are summarised in Table 3. Differences in pre- and postoperative WBC and eosinophil count, sedimentation rate and CRP were not statistically significant in women. On the other hand, although the change in WBC count and CRP value was not statistically significantly different in males, the difference in the eosinophil count was statistically significant, with a negative correlation ($p = 0.002$). The difference in sedimentation rate was also statistically significant and demonstrated a positive correlation ($p = 0.005$) (Table 3). In other words, postoperative sedimentation rate decreased in men and the change was 2.66 ± 4.76 mm/h, which was statistically significantly different ($p < 0.05$) (Table 3). When the difference in the rheumatoid factor was evaluated pre- and postintervention, no statistically significant changes were found in either gender ($p < 0.05$) (Table 3).

Table 3. Pre- and postoperative changes in whole blood and serological parameters by gender

Parameter	*Pre-operative value*	*Postoperative value*	t-*value*	p-*value*
WBC (× 10^3 cells/µl)				
Female	6.87 ± 1.55	6.65 ± 1.53	1.375	0.173
Male	6.68 ± 1.96	6.37 ± 1.41	1.262	0.217
Neutrophils (× 10^3 cells/µl)				
Female	3.99 ± 1.30	3.99 ± 1.30	–0.985	0.328
Male	4.35 ± 1.39	4.34 ± 1.38	1.116	0.273
Eosinophils (× 10^3 cells/µl)				
Female	0.51 ± 1.03	0.51 ± 0.98	0.000	
Male	0.96 ± 2.28	1.37 ± 2.57	–3.479	1.000
Basophils (× 10^3 cells/µl)				0.002*
Female	0.06 ± 0.16	0.04 ± 0.07	1.199	0.235
Male	0.33 ± 0.74	0.09 ± 0.22	1.740	0.093
Haemoglobin (g/dl)				
Female	13.17 ± 0.93	13.05 ± 0.89	1.000	0.324
Male	15.26 ± 1.51	15.76 ± 1.32	–2.584	0.022*
Haematocrit (%)				
Female	40.64 ± 2.77	39.78 ± 2.76	1.837	0.075
Male	45.29 ± 4.08	49.16 ± 9.74	–1.650	0.121
Thrombocytes (10^3 cells/µl)				
Female	260.80 ± 61.55	239.31 ± 88.02	1.551	0.129
Male	186.11 ± 33.16	193.72 ± 38.98	–2.061	0.055
Sedimentation rate (mm/h)				
Female	22.08 ± 9.42	24.41 ± 16.79	–1.407	0.164
Male	11.33 ± 5.54	8.66 ± 3.07	3.065	0.005*
CRP (mg/dl)				
Female	1.24 ± 1.25	1.30 ± 1.26	–1.540	0.128
Male	2.84 ± 1.62	2.75 ± 1.85	0.526	0.603
Rheumatoid factor (IU/ml)				
Female	6.80 ± 5.83	6.41 ± 5.63	0.853	0.396
Male	7.11 ± 4.79	7.24 ± 2.50	–0.205	0.839

WBC: white blood cells; CRP: C-reactive protein.

Discussion

The field of use of cyanoacrylate (CA) in medical treatment has gradually increased since its discovery.[13,14] It has been used in ophthalmological operations, cosmetic procedures, dental applications and acute bleeding, with the aim of stopping the bleeding and attaching the tissues. Also, endoscopic injection of CA has been widely and safely used in order to cease gastric variceal bleeding.[9] Recently it has been administered via the endovenous route for the treatment of varicose veins and superficial venous insufficiency without the need for tumescent anaesthesia[11] or thermal energy, with increasing evidence proving that it could be an appropriate agent for the treatment of peripheral varicose veins.[10,15]

The mechanism of effect of NBCA is simple; it stimulates polymerisation when it comes into contact with blood and plasma, hence causing an obstruction of the vein in which it is administered. This occurs in three steps: the initiation phase lasts approximately 10 seconds and the tensile force increases rapidly; the second phase lasts for approximately one minute and creates a steady tensile force; the last phase is completion of the polymerisation and a strong tensile force is obtained.[16]

Almeida *et al.* closed the truncal vein of pigs using CA and after a follow-up period of 60 days, found no thrombus obstructing the lumen of the vein on sonography or histology. Instead he observed a chronic foreign body reaction against NBCA.[15] When the tissues were examined, they observed an inflammatory reaction and the formation of giant cell foreign bodies, followed by the development of intraluminal fibrosis.[15]

Endovenous NBCA application has been well tolerated in

patients. The results of our administration are similar.

Inflammation is activated when an organism is triggered by stimulants. An acute inflammatory reaction is characterised by neutrophil predominance in the region of the event.[17] Neutrophil and leukocyte counts in the blood are increased during acute inflammation. No statistically significant changes were detected between pre- and postoperative counts of either WBC or neutrophils in our study. Acute inflammation in the endovenous administration of NBCA was therefore most likely localised in the vein wall and surrounding tissues. There are reports in the literature demonstrating that NBCA causes a local inflammation,[10,12] but there are no studies that have evaluated the systemic response.

The acute-phase response includes endocrinological, neurological and immunological events.[18] Proteins, whose levels increase or decrease during this period, are called acute-phase proteins or acute-phase reactants.[19] Change in the levels of acute-phase proteins demonstrate the presence and severity of inflammation.[20]

Cytokines are released as a response to stress by inflammatory cells such as neutrophils and macrophages. Interleukine-6, interleukine-1 and tumour necrosis factor-α induce CRP secretion from the hepatocytes.[21] CRP has a pro- and anti-inflammatory effect. Its pro-inflammatory effects result in the activation of the complement system and the induction of tissue factor and inflammatory cytokines from the monocytes, but its most important role is its anti-inflammatory effect.[22]

Erythrocyte sedimentation rate (ESR) is a frequently used test for the evaluation of acute-phase response.[23] ESR increases from the start of the inflammation and resolution may take up to a month.[24] In our study, no statistically significant change was seen in the CRP level and sedimentation rate between the pre- and post-procedure states of endovenous NBCA use. Changes in sedimentation rate from the pre- to the postoperative values by gender were statistically significant in the male patients ($p < 0.05$); however they were within the normal range, and postoperatively showed a decreasing trend. CRP levels were similar between the pre- and post-procedural states by gender and in the overall group of patients. Since there was no change demonstrated in the CRP level and sedimentation rate, and in the neutrophil and WBC counts, it can be concluded that NBCA did not cause an acute systemic inflammatory response.

Sensitivity has been detected in patients when NBCA was used to repair skin wounds, and also in individuals who were occupationally exposed to CA.[25] In a study by Quinn *et al*., eosinophilic inflammation was detected at a rate of approximately 2% following NBCA use in the closure of intracranial arteriovenous malformations. The authors reported that no history of sensitivity against or exposure to CA was previously detected in those patients.[25] When our patients was evaluated, no statistically significant changes in the pre- and postoperative eosinophil and basophil counts were found. From these results, we concluded that NBCA caused no allergic reaction in this patient group.

Conclusion

The greatest advantage of the endovenous medical ablation method using NBCA is that tumescent anaesthesia and thermal energy are not necessary. In addition, since it causes no systemic allergic or acute inflammatory reaction, it appears safe to use. However, we suggest that evaluations should be performed in a larger group of patients to confirm the results.

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Significant financial stress associated with 13-fold higher odds of having a heart attack

Significant financial stress is associated with a 13-fold higher odds of having a heart attack, according to research presented at the 18th Annual Congress of the South African Heart Association.

'The role of psychosocial factors in causing disease is a neglected area of study in South Africa, perhaps because there are so many other pressing health challenges such as tuberculosis and HIV,' said lead author Dr Denishan Govender, associate lecturer, University of the Witwatersrand, Johannesburg.

'The INTERHEART study showed that psychosocial factors are independently associated with acute myocardial infarction (heart attack) in Africa but as far as we are aware there are no other published local data,' said last author Professor Pravin Manga, professor of cardiology, University of the Witwatersrand.

This study included 106 patients with acute myocardial infarction who presented to a large public hospital in Johannesburg. A control group of 106 patients without cardiac disease was matched for age, gender and race. All participants completed a questionnaire about depression, anxiety, stress, work stress and financial stress in the previous month. The Likert scale was used to grade the experience of each condition.

Regarding financial stress, patients were graded with no financial stress if they were coping financially; mild financial stress if they were coping financially but needed added support; moderate financial stress if they had an income but were in financial distress; and significant financial stress if they had no income and at times struggled to meet basic needs. Levels of psychosocial conditions were compared between groups and used to calculate associations with having a heart attack.

Self-reported stress levels were common, with 96% of heart attack patients reporting any level of stress, and 40% reporting severe stress levels. There was a three-fold increased risk of myocardial infarction if a patient had experienced any level of depression (from mild to extremely severe) in the previous month compared to those with no depression.

Both work stress and financial stress were associated with a higher risk of acute myocardial infarction. The odds of myocardial infarction was 5.6 times higher in patients with moderate or severe work stress compared to those with minimal or no stress. Patients with significant financial stress had a 13-fold higher odds of having a myocardial infarction.

Dr Govender said: 'Our study suggests that psychosocial aspects are important risk factors for acute myocardial infarction. Often patients are counselled about stress after a heart attack but there needs to be more emphasis prior to an event. Few doctors ask about stress, depression or anxiety during a general physical and this should become routine practice, like asking about smoking. Just as we provide advice on how to quit smoking, patients need information on how to fight stress.'

Professor Manga said: 'There is growing recognition that many developing countries are experiencing an increasing prevalence of chronic diseases of lifestyle such as myocardial infarction, and South Africa is no exception. Our study shows that psychosocial aspects are an area of cardiovascular prevention that deserves more attention.'

Dr David Jankelow, chairman of the SA Heart 2017 congress, commented: 'We know that the depressed cardiac patient is at greater risk. We as clinicians need to identify them much earlier, so that they can be referred for appropriate intervention. Cardiac rehabilitation together with counselling and reassurance will play an important role as well.'

Professor Fausto Pinto, ESC immediate past president and course director of the ESC programme in South Africa, said: 'Psychosocial factors including stress at work, depression and anxiety contribute to the risk of developing cardiovascular disease and having a worse prognosis. European prevention guidelines say that psychosocial risk-factor assessment should be considered in people with, or at high risk of, cardiovascular disease to identify possible barriers to lifestyle change or adherence to medication.'

Source: European Society of Cardiology Press Office