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EDITORIAL

Circulating endothelial and progenitor cells: Evidence from acute and long-term exercise effects

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Abstract

Circulating bone-marrow-derived cells, named endothelial progenitor cells (EPCs), are capable of maintaining, generating, and replacing terminally differentiated cells within their own specific tissue as a consequence of physiological cell turnover or tissue damage due to injury. Endothelium maintenance and restoration of normal endothelial cell function is guaranteed by a complex physiological procedure in which EPCs play a significant role. Decreased number of peripheral blood EPCs has been associated with endothelial dysfunction and high cardiovascular risk. In this review, we initially report current knowledge with regard to the role of EPCs in healthy subjects and the clinical value of EPCs in different disease populations such as arterial hypertension, obstructive sleep-apnea syndrome, obesity, diabetes mellitus, peripheral arterial disease, coronary artery disease, pulmonary hypertension, and heart failure. Recent studies have introduced the novel concept that physical activity, either performed as a single exercise session or performed as part of an exercise training program, results in a significant increase of circulating EPCs. In the second part of this review we provide preliminary evidence from recent studies investigating the effects of acute and long-term exercise in healthy subjects and athletes as well as in disease populations.

Key words: Circulating endothelial cells; Circulating progenitor cells; Exercise; Cardiovascular disease

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CIRCULATING ENDOTHELIAL AND PROGENITOR CELLS

The process of blood vessel formation occurs by two different mechanisms, angiogenesis and vasculogenesis. Angiogenesis describes blood vessel growth from existing blood vessels by sprouting of differentiated endothelial cells or intussusceptions of existing capillaries[1,2]. In contrast, vasculogenesis is defined as blood vessel

growth from *in situ* differentiating angioblasts[3]. Until recently, it has been assumed that vasculogenesis is limited to embryogenesis. For the first time in 1997, Asahara *et al*[4] described the existence of endothelial cells in the peripheral blood of adults derived from the bone marrow, and confirmed the role of vasculogenesis during the process of postnatal neovascularization. Hematopoietic stem cells that give rise to blood cells and move between bone marrow and peripheral blood are the best-characterized adult stem cells in humans. This circulating bone-marrow-derived cell population has been named endothelial progenitor cells (EPCs)[5]. There are at least two different types of EPCs population, early and late. Early EPCs are usually referred to as the angiogenic EPC population obtained from short-term cultures of 4-7 d. Late EPCs, often called outgrowth EPCs, have different growth patterns and are usually obtained from long-term cultures of at least 2-4 wk[6]. These cells are capable of maintaining, generating, and replacing terminally differentiated cells within their own specific tissue as a consequence of physiological cell turnover or tissue damage due to injury[7].

Endothelial cell injury, after tissue ischemia or vascular injury, initiates physiological processes of reparation and regeneration. The initial step is the mobilization of EPCs from the bone marrow into peripheral blood, which is followed by the recruitment of EPCs to the site of tissue ischemia or vascular injury (Figure 1). Locally, vasculogenesis occurs after EPC adhesion and migration into the newly formed vascular network and differentiation into mature endothelial cells[8]. The pathophysiology mentioned above is critical in terms of endothelium maintenance and restoration of normal endothelial cell function.

The current literature suggests that adult stem cells generate differentiated cells beyond their own tissue boundaries, a process termed "developmental plasticity". Circulating EPCs play two major roles, endothelial healing and neoangiogenesis[9,10].

EPCs AND ENDOTHELIAL DYSFUNCTION

For more than 10 years researchers as well as clinicians have focused on understanding the physiological and pathophysiological role of the EPCs in the cardiovascular system and in cardiovascular disease, because endothelial dysfunction has been established as an independent prognostic risk factor for cardiovascular disease[11,12]. Although there are no clear definition criteria for accurate identification of EPCs so far, there have been several studies indicating the important role of EPCs in restoring endothelial damage[13]. Decreased numbers of EPCs have been associated with endothelial dysfunction and high cardiovascular risk[5,14].

Promotion of recruited bone-marrow-derived EPCs is the primary mechanism for endothelial replacement in areas of vascular damage as demonstrated in animal models. In these experimental ischemic injuries, bone-marrow-derived cells play an important role in vascular repair and regeneration enhancing tissue recovery[15-17].

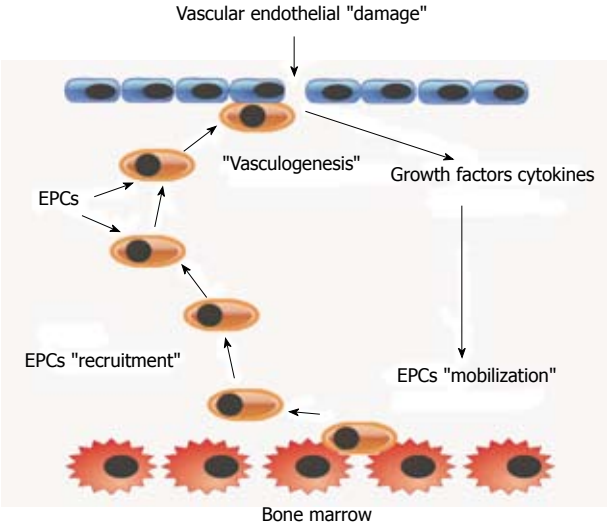

Figure 1 An illustrative model of vasculogenesis after vascular endothelial damage mediated by bone marrow endothelial progenitor cell mobilization and recruitment. EPC: Endothelial progenitor cell.

EPCs are present in peripheral blood circulation of healthy adult subjects, although in small numbers and are responsible for vascular and endothelial repair after tissue damage[18]. A decrease in EPC levels was shown to inversely correlate with the occurrence of endothelial dysfunction[5,19].

EPCs AND AGING

It has been also documented that EPCs are significantly reduced in elderly populations[20], and appear to have elevated apoptotic susceptibility[21]. The number and function of early EPCs isolated from the peripheral blood of 20 healthy young and 20 old (61 ± 2 years) individuals have been investigated by Heiss *et al*[22]. Early EPCs from the old subjects were found to be significant impaired in terms of fundamental functional features like proliferation, migration and survival, although no quantitative differences in EPCs were observed. Chronic treatment with bone-marrow-derived progenitor cells from young non-atherosclerotic ApoE$^{-/-}$ mice prevents atherosclerosis progression in ApoE$^{-/-}$ mice recipients despite persistent hypercholesterolemia. In contrast, treatment with bone marrow cells derived from older ApoE$^{-/-}$ mice is much less effective[23]. Similarly, transplantation of bone-marrow-derived EPCs from young, but not old donor mice prevented a decline in the angiogenic platelet-derived growth factor signaling and cardiac angiogenesis in an aging murine model[24]. Despite these well-documented experimental studies on EPCs in aging populations, the mechanisms are still unknown and further research is needed.

EPCs AND CORONARY HEART DISEASE

In human studies, circulating EPC levels have been inves-

tigated as surrogate markers of coronary artery disease (CAD) severity and indices of clinical outcome, with significant results[25-28].

The activity and migratory capacity of EPCs is reduced in patients with coronary heart disease[29]. Furthermore it has been shown that EPCs enhance angiogenesis, promote vascular repair, improve endothelial function, inhibit atherosclerosis and increase ventricular function after myocardial infarction[5,9,30-32]. All these findings indicate that the number of EPCs may be a marker of cardiovascular risk. EPCs levels were also inversely correlated with the occurrence of in-stent restenosis[33].

EPCs AND CHRONIC HEART FAILURE

Very few research groups have studied circulating EPCs levels in chronic heart failure (CHF). Specifically, it has been shown that EPC mobilization occurs in a biphasic pattern in CHF; increased in mild stages, and depressed in advanced CHF[34,35]; possibly due to the myelosuppressive role of cytokines such as tumor necrosis factor-α in severe CHF. A significant progressive increase of EPCs was noted in patients admitted with acute exacerbation concomitantly with their clinical amelioration during hospitalization[36].

Interestingly, Geft *et al*[35] have studied early and late apoptotic progenitor cells in CHF, showing that severe heart failure patients exhibited higher numbers of late apoptotic progenitors, and there was a significant association of the latter cells with disease severity. However, in another clinical study, the authors reported that there was no correlation between $CD34^+$ circulating cells and New York Heart Association (NYHA) functional class[37].

Further research is needed to clarify the clinical significance of EPCs levels and their role in CHF patients in relation to acute exacerbations and disease severity.

EPCs AND LEFT VENTRICULAR ASSIST DEVICES

Over the past 4 years a few studies investigated the role of left ventricular assist device (LVAD) implantation in the number of EPCs in patients with end-stage CHF (NYHA class Ⅲ or Ⅳ). In a recent study, Jahanyar *et al*[38] have demonstrated that LVADs cause a significant increase of stem cell factor and its receptor (c-kit) gene expression, which coincided with a surge of mast cells after ventricular unloading. In another study[39], a significant increase in EPCs was also reported after LVAD implantation.

Both studies were limited by the small number of participants and the lack of an adequate control group. In the study of Jahanyar *et al*[38] the patients' EPCs were compared to tru-cut biopsies of donor hearts, while in the study of Manginas *et al*[39], the control group comprised patients who were ineligible for LVAD implantation.

In addition, in an experimental study[40], the research group found that the intramuscular injection of EPCs [in particular KLS cells ($Lin^-/c\text{-}kit^+/Sca1^+$)] in the LV-unloading heart of rodents, may have a protective effect against cardiac systolic dysfunction and myocardial atrophy. The latter study suggests that this intervention may have a clinical potential as a combination therapy together with LVAD implantation.

Besides the nature of the study populations with the methodological flow limiting results, it seems that LVAD implantation increases EPC levels.

EPCs AND PULMONARY ARTERIAL HYPERTENSION

Endothelial dysfunction is strongly involved in the pathophysiology of pulmonary arterial hypertension (PAH)[41]. For this reason a growing interest has been recently raised in the role of EPCs in PAH. In a study of Smadja *et al*[42], the number of circulating endothelial cells was significantly higher in 10 patients with irreversible PAH than in 16 patients with reversible PAH and five control subjects, while progenitor cells did not differ among the groups. To make things more confusing it has also been reported that a significant decrease was observed in circulating EPCs in 20 patients with idiopathic PAH compared to 20 healthy controls[43]. Accordingly, Hansmann *et al*[44] reported that EPC numbers were 50% lower in PAH subjects versus matched controls.

In contrast with previous studies mentioned above it has been reported that EPCs were increased in patients with PAH compared with controls[45]. In a recent clinical trial, where nine patients with PAH, nine patients with chronic thromboembolic pulmonary hypertension (CTEPH), and seven subjects with normal pulmonary arterial pressure were enrolled, the researchers concluded that EPCs were significantly increased in PAH patients compared to CTEPH and controls[46].

The results from the above studies appear conflicting, thus, further research is needed to clarify the role of EPCs in PAH. Research on EPCs should target on the different PAH stages, and the PAH diagnosis duration that might differentiate in terms of number and function.

EPCs AND CRITICAL ILLNESS

Recent innovative studies have shown that mobilization of EPCs occur in critically ill patients and are significantly associated with clinical outcome and prognosis[47-51].

In 2001, an increased number of EPCs in patients with sepsis and septic shock was found compared to healthy subjects[49]. These findings were confirmed in a more recent study by Rafat *et al*[47]. They reported that after studying 32 intensive care unit patients with sepsis, 15 patients without sepsis and 15 healthy controls, the number of EPCs was not only significantly higher in septic patients compared to non-septic patients and controls, but was also associated with survival. In a methodologically similar study, Burnham *et al*[48] have shown that increased number of EPCs was highly correlated with

improved survival in patients with early acute lung injury. In addition, in a prospective study enrolling 44 patients with ventilator-associated pneumonia and sepsis, the research group concluded that EPCs count on day 1 was correlated with survival[50]. These studies suggest that patients with sepsis appear to present with elevated EPCs numbers compared to healthy controls, and furthermore, that EPCs levels are strongly correlated with outcome.

EPCs AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

To the best of our knowledge, only a few studies[52-54] have investigated the number of EPCs in patients with chronic obstructive pulmonary disease (COPD). Methodological differences might have played a significant role in the fact that the studies had conflicting results. Peinado *et al*[52] conducted dissection on pulmonary arteries of lung specimens of 15 patients undergoing lung resection because of carcinoma and compared the EPC numbers in nine subjects with moderate to severe COPD to the six subjects free of COPD. The authors concluded that EPCs were significantly greater in number in COPD patients.

In contrast to that study, two other controlled studies[53,54] reported lower levels of EPCs in blood samples from COPD patients compared to controls. The number of EPCs was also strongly correlated to disease severity for both studies. In a study by Sala *et al*[55], the authors investigated the response of EPCs to episodes of exacerbation of COPD (ECOPD). After studying 35 patients hospitalized because of ECOPD, 44 COPD patients, 10 smokers free of COPD and 10 healthy non-smokers, they found a higher level of EPCs in the ECOPD group compared to the other groups. Just recently, it has been shown that there is an impaired EPC mobilization and colony-forming capacity in COPD patients with stage I and II lung cancer undergoing thoracic surgery[56]. It seems that more evidence is necessary to understand better the role of EPCs in COPD due to the inconclusive results mentioned above.

EPCs AND OBSTRUCTIVE SLEEP APNEA

Four controlled studies[57-60] have been conducted to investigate the number of EPCs in patients with obstructive sleep apnea (OSA), who lacked cardiovascular disease and were free of any other known cardiovascular risk factor. All studies had a small number of participants and reported conflicting results. El Solh *et al*[60] by studying 14 subjects with OSA documented higher numbers of EPCs compared to 10 healthy controls. They also reported that an 8-wk treatment with continuous positive airway pressure (CPAP) therapy significantly reduced the levels of EPCs in the OSA patient group. The same research group a year later confirmed the above outcome by enrolling 35 OSA patients on 8 wk nasal CPAP therapy[58].

In another study that included 13 OSA patients and 13 controls, there was a reduced number of EPCs in patients with OSA compared to controls[59]. However, other researchers found no significant differences in EPCs between OSA patients and controls[57].

The conflicting results of the above studies need further investigation with larger numbers of study participants before conclusions can be made for the possible role of EPCs in OSA. Disease severity might play a significant role in the EPCs level and should be further assessed.

EPCs AND DIABETES

In diabetic patients the EPC levels are significantly reduced compared to non-diabetic controls. Loomans and colleagues reported that the EPCs numbers were decreased in patients with type I diabetes, compared to EPCs levels in healthy subjects[61]. Enrolling 74 patients with type I diabetes, EPCs counts were significantly lower in these patients compared to 80 healthy controls[62].

Similarly, other studies have also demonstrated that EPCs levels were lower in patients with diabetes mellitus type II compared to healthy controls[63-65]. Treatment with strict glycemic control and total cholesterol improvement increased EPCs numbers[65]. There is strong evidence that patients with diabetes types I and II appear to have lower EPCs numbers compared to healthy controls. Further research is needed demonstrating the beneficial effects of the potential increase in EPCs by certain therapeutic measures (diet, exercise training, antidiabetic drug treatment, *etc*.).

EPCs AND CEREBROVASCULAR DISEASE

In a study of Ghani *et al*[66], there was a significant difference in EPC counts between stroke patients (acute stroke: median 4.75, range 0-33; stable stroke: median 7.25, range 0-43) and control subjects (median 15.5, range 4.3-50), independent of age. In contrast, Yip *et al*[67] demonstrated that the levels of circulating EPCs did not differ between patients with ischemic stroke and normal control subjects. The authors also reported that in patients with acute ischemic stroke, the EPCs levels were significantly higher than in subjects at high cerebrovascular risk, but appeared to be lower in patients with severe neurological impairment. The research group stated that the inconsistency of their findings with the results of Ghani *et al*[66] was due to the difference in the time interval for blood sampling between the studies.

There was a significant decrease in circulating $CD34^+$ cell levels in 25 patients with a history of atherothrombotic cerebral ischemic events compared with age-matched controls[68]. Colony forming units (CFUs) and outgrowth cell population as a subset of EPCs were significantly reduced in 75 patients with acute stroke, compared with 45 patients with chronic stroke and 40 age-matched control subjects. Moreover, patients with large artery atherosclerosis had much lower CFU numbers and functional activities

than the ones with cardioembolism[69].

It has also been reported that the increase in circulating EPC levels after acute ischemic stroke is associated with good functional outcome and reduced infarct growth, suggesting that EPCs might participate in neurorepair after ischemic stroke[70]. There are convincing data that ischemic stroke is strongly correlated with low EPC levels and that levels are strongly correlated with functional outcome in acute ischemic stroke.

EPCs AND PERIPHERAL ARTERIAL DISEASE

Little information is available on EPC mobilization in patients with peripheral arterial disease (PAD). In 2008, Delva *et al*[71] studied the number of EPCs by different methods in a carefully selected group of 45 patients with CAD along with 24 healthy subjects. In patients with PAD, by utilizing the dual-binding method, the number of circulating EPCs was significantly increased compared to that in healthy controls. On the contrary, while using fluorescence-activated cell sorting analysis the results were different, both $CD34^+$ and $CD133^+$ cell counts were significantly decreased compared to controls. The use of different methods in data collection may explain the discrepancy. Finally, CFUs were significantly increased in PAD compared to healthy subjects[71].

After studying 48 PAD patients and 22 patients without PAD the researchers concluded that EPC mobilization occurred in PAD and showed a biphasic response, with elevated EPC levels in the moderate phase and reduced EPC levels in the advanced phase. EPC levels were also associated with the levels of novel circulating biomarkers and several aspects of PAD, including the severity, progression and disease outcome[72].

As a result of the limited number of studies, further research is needed on the levels of EPCs in patients with PAD. It seems however, that there is an increase of EPC levels in the moderate phase and a decrease in the advance phase of PAD.

EPCs AND ARTERIAL HYPERTENSION

In the very early stage of hypertension a significant increase in circulating progenitor cells is associated with reactive oxygen species and oxidative stress[73]. Vasa *et al*[19], after studying patients with CAD concluded that the migratory capacity of EPCs was reduced in those patients with hypertension, although their total number did not change significantly.

Additionally, only recently it has been demonstrated that the *in vivo* endothelial repair capacity of early EPCs is substantially impaired in patients with newly diagnosed pre-hypertension and hypertension as their only cardiovascular risk factor[74]. Increased senescence of early EPCs in pre-hypertensive and hypertensive patients was related to abnormal EPCs endothelial repair capacity. In the same study there was not a significant difference in the numbers of EPCs and endothelial apoptotic microparticles in pre-hypertensive and hypertensive patients when compared with healthy controls. From this study emerges evidence that the endothelial repair capacity of early EPCs is substantially impaired in hypertensive patients.

EPCs AND OBESITY

It is well established that obesity is associated with decreased numbers of EPCs[75-79]. The number of circulating EPCs is lower in obese compared with overweight and normal weight subjects, while EPCs colony forming capacity is blunted in overweight and obese compared with normal weight subjects[76]. Tobler *et al*[77] also stated that reduced numbers of EPCs along with their premature senescence might contribute to the development and progression of vascular dysfunction in obesity. Furthermore, the function of EPCs in obesity is impaired either by the impaired ability of circulating EPCs to release proangiogenic growth factors compared with normal weight adults and by the lower EPC resistance to an apoptotic stimulus in overweight and obese compared to normal weight[78]. Interestingly, low EPCs levels[75] and their functional deficiency[79] can be reversed after significant weight reduction.

A summary of the above studies of EPCs in different disease populations is reported in Table 1.

PHYSICAL ACTIVITY, EXERCISE TRAINING AND ENDOTHELIAL FUNCTION

It is well recognised that physical activity has significant beneficial effects on overall health, and especially on cardiovascular morbidity and mortality. Physical inactivity is an independent risk factor for the development of coronary heart disease, stroke and peripheral vascular disease[80].

Regular physical activity significantly attenuates the atherosclerotic process by reducing atherosclerotic risk factors, retarding arterial wall aging[81,82], delaying development of endothelial dysfunction and preserving vascular function[83]. Furthermore, physical training reduces vascular oxidative stress, increases the activity of endothelial nitric oxide synthase (eNOS)[84] and results in increased blood flow to oxidative skeletal muscle fibers[85].

Accordingly, the beneficial effects of exercise have been reported in patients with CAD as part of the secondary prevention[86,87]. It is well known that physical training improves endothelial function and exercise capacity in patients with CAD[88], CHF[89] and PAD[90]. Exercise is also associated with improved body weight, blood pressure, insulin sensitivity and hemostatic and inflammatory variables[91,92]. High-intensity interval training is a relative novel alternative modality of exercise in metabolic syndrome[93], coronary heart disease[94] and in CHF patients[95-97], allowing more intense stimuli in the peripheral muscles. The addition of strength training has been also shown to confer significant improvement in endothelial function[98,99] and peripheral microcirculation[100] in CHF patients.

Table 1 Summary of endothelial progenitor cell levels in different disease populations

Disease	Results	Comments	Ref.
Aging	↓ EPCs proliferation ↓ EPCs migration ↓ EPCs survival		[20,22]
Coronary heart disease	↓ EPC activity ↓ EPC migratory capacity		[29]
CHF	↑ EPC levels in mild stages[34,35] ↑ EPC levels in acute exacerbation[36] ↑ Late apoptotic progenitors[35] ↓ EPC levels in advanced stages[34,35]		[34-36]
LVADs	↑ EPC levels		[38,39]
PAH	↑ EPC levels[42,45,46] ↓ EPC levels[43,44]	Conflicting results	[42-46]
Critical illness	↑ EPC levels in sepsis and septic shock[47,49] ↑ EPC levels in early acute lung injury[48]		[47-49]
COPD	↑ EPC levels[52] ↓ EPC levels[53,54] ↑ EPC levels in exacerbation of COPD[55] ↓ EPC mobilization and colony-forming capacity[56]	Conflicting results	[52-56]
OSA	↑ EPC levels[58,60] ↓ EPC levels[59] - No difference[57]	Conflicting results	[57-60]
Diabetes mellitus type I and Ⅱ	↓ EPC levels		[61-65]
Cerebrovascular disease	↓ EPC levels in stroke[66] - No difference in ischemic stroke[67] ↑ EPC levels in acute ischemic stroke[67] ↓ EPC levels in atherothrombotic cerebral ischemic event[68] ↓ EPC colony forming in acute stroke[69]		[66-69]
PAD	↑ EPC levels in moderate phase ↑ EPC levels in advance phase		[71,72]
Arterial hypertension	↑ EPC levels in early stage of hypertension[73] ↓ EPC migratory capacity in CAD and hypertension[19] - No difference on EPC levels in pre-hypertensive and hypertensive[74]		[19,73,74]
Obesity	↓ EPC levels[75-77] ↓ EPC colony forming capacity[76]		[75-79]

EPC: Endothelial progenitor cell; CHF: Chronic heart failure; LVAD: Left ventricular assist device; PAH: Pulmonary arterial hypertension; COPD: Chronic obstructive pulmonary disease; OSA: Obstructive sleep apnea; PAD: Peripheral arterial disease; CAD: Coronary artery disease.

It has become common knowledge that exercise training has a significant therapeutic role in a vast majority of diseases. A structured exercise training program, and more specifically a combination of aerobic exercise (continuous or high-intensity interval training) with or without the addition of strength training can significantly attenuate the atherosclerotic process through its beneficial effects on endothelial function[93,95,98-100]. However, there is growing interest concerning the role of exercise training on EPCs that may interact with endothelium function; this issue is currently under investigation from several research groups in both healthy subjects and diseases.

EFFECTS OF EXERCISE TRAINING ON EPCs

Laufs *et al*[101] in 2004 were the first research group to demonstrate that physical activity leads to an increased number of circulating EPCs in mice after 28 wk of running wheels. This effect occurred rapidly (7 d after training) and was sustained for at least 4 wk, providing evidence that EPC numbers can be increased by nearly threefold by exercise training. These findings were confirmed by another research group in a human study in which middle aged and older subjects following a 3 mo training program of walking, at moderate intensity, increased circulating angiogenic cell (CAC) migratory capacity by 50%[20]. Accordingly, Yang *et al*[102] showed that the number and activity of circulating EPCs of 10 older and 10 young sedentary healthy men were increased after 3 mo regular exercise. However, the increased number and activity of circulating EPCs of older sedentary healthy men was higher compared to the younger group. In contrast, in a study of 20 healthy men who followed a 6-wk interval exercise training program, [moderate (9 subjects) or high intensity (11 subjects)], there was no significant effect on EPC number in both groups, even though there was an improvement of vasoconstrictor function[103].

Furthermore, a study of 182 children (aged 11.1 ± 0.7 years) showed that physical activity by means of daily school exercise lessons can increase the number of circulating progenitor cells[104]. More interestingly, EPC numbers decreased significantly after 10 d of detraining in highly active older men, even lower than the level of low-active (sedentary) men[105]. These findings agree with the fact that sustained physical activity is necessary to preserve improved endothelial function for maintaining long-term training effects[106].

In an animal study, 8 wk of aerobic training in mice with advanced atherosclerotic lesions showed no improvement in atherosclerosis, whereas mice with early lesions benefited. The authors suggest that the impact of exercise on atherogenesis is primarily to retard the progression to advanced lesions, rather than reversing advanced lesions. Interestingly, the level of EPCs decreased, along with proinflammatory cytokines in response to exercise[107].

In another experimental study conducted in the early phase following traumatic brain injury in rats, the exercise group compared to the control group enhanced significantly proliferation of neural stem cells (NSCs) around the damaged area[108].

Despite the significant experimental study of Laufs *et al*[101], Luk *et al*[109] showed that there was no significant increase in CD34/KDR$^+$ EPCs after an 8-wk exercise training programme on 32 patients with CAD compared to controls. In contrast, in a recent uncontrolled study by

Cesari *et al*[110], there was a significant increase in EPCs and a significant decrease in proinflammatory biomarkers, in patients with acute coronary syndrome, occurring after a 30-d period of cardiac rehabilitation (3 sessions per week of endurance training on a cycle ergometer, at 60%-70% of individual VO_2 level obtained at peak exercise during baseline symptom-limited cardiopulmonary exercise testing). Because of the conflicting results and the small number of studies, more human studies are needed to clarify the possible beneficial effects of exercise on EPCs in CAD.

EPC levels [assessed as $CD34^+$ cells coexpressing AC133 and vascular endothelial growth factor receptor 2 (VEGFR2), and as endothelial CFUs (e-CFUs)] were also evaluated in chronic renal failure patients on hemodialysis after a 6-mo walking exercise program. This study showed that there was not a significant change in $CD34^+$ or $CD34^+/AC133^+/VEGFR2^+$ cell numbers, but there was a significant change in e-CFUs[111].

A significant enhancement of circulating EPCs after 8 wk of supervised exercise training has also been demonstrated in CHF patients. In that study, 8 wk of detraining led to baseline EPC levels[112]. In a recent study by Van Craenenbroeck *et al*[113] similar results have emerged after investigating the effect of 6 mo exercise training in CHF, compared with a no exercise CHF group and a no exercise group of healthy subjects. The authors reported a reverse effect of exercise training on circulating angiogenic cell dysfunction and an increase in EPCs. An analogous increase in EPC numbers was found, after short-term exercise training (3 wk) in 14 CHF patients[114]. The exercise program was a combination of calisthenics and aerobic exercise with an intensity up to 75%-85% of the maximum heart rate attained in the exercise test. The authors reported that even a relatively short-term exercise training program significantly improved the serum ability to support viability of EPCs as well as upregulation of proteins participating in LV remodeling.

Similarly, 37 CHF patients (LV ejection fraction 24% ± 2%) were randomly assigned to 12 wk of exercise training (n = 18) or sedentary lifestyle (n = 19). Exercise training increased the number of $CD34^+$ progenitor cells from 1094 ± 677 to 1450 ± 798 cells/mL blood in the training group (P = 0.032 *vs* control). The number of $CD34^+/KDR^+$ EPCs was found to be augmented from 100 ± 127 to 183 ± 156 cells (P = 0.014 *vs* control) and their migratory capacity by 224 ± 263 *vs* -12 ± 159 CPCs/1000 plated CPCs in controls (P = 0.03)[115].

The most recent paper on the effect of exercise training in patients with CHF is the one published by Mezzani *et al*[116]. Patients (n = 30) with NYHA class Ⅱ were allocated to either an aerobic 3-mo exercise training group or a control group, while seven age-matched healthy subjects were also studied. In addition to the previous studies, the authors reported that the numbers of EPCs, even though they did not differ between patient groups at baseline, significantly increased in the CHF training group, reaching values similar to those of healthy controls, while the difference between CHF controls and healthy controls did not reach statistical significance. Additionally, the levels of EPCs remained unchanged in the control patient group.

In a randomized controlled clinical trial, 40 patients with PAD were allocated to either an exercise or a control group. The intervention group followed a standardized training program twice a week for 6 mo. The initial duration included 35 min of intermittent walking, which was increased by 5 min each session until 50 min of intermittent walking was achieved. EPC levels were significantly increased and asymmetric dimethylarginine levels were decreased in the exercise group compared with the controls. The authors suggested an enhanced angiogenesis and improved endothelial function that might contribute to cardiovascular risk reduction[117].

The first study on the effect of exercise training in overweight and obese patients has recently been published by Cesari *et al*[118]. Even though the study had a few methodological limitations, the authors reported a significant increase in all the three groups of EPCs ($CD34^+/KDR^+$: +33.3%; $CD133/KDR^+$: +35%; $CD34^+/CD133^+/KDR^+$: +35.7%) after a 3 mo exercise intervention program, compared to baseline measurements.

The underlying mechanisms of the effect of exercise training on EPC levels needs further investigation, but taken together with the existing data, it has been suggested that physical exercise increases NO bioavailability[119], and in parallel with this fact, the effect of physical activity on EPCs is markedly reduced after inhibition or deletion of eNOS, which suggests an NO-dependent increase in EPCs in response to exercise[101,113]. Additionally, it has been reported that physical exercise may increase EPC numbers by prolonging their lifespan. Data derived from cultured EPCs have indicated that the observed EPCs enhancement in the circulation and the bone marrow could be explained partly by antiapoptotic effects of physical activity on EPCs and potentially their progeny[101]. The extra muscle stress that is additive to hypoxic stress and leads to a hypoxia-induced factor-1-mediated upregulation of both VEGF and stromal-cell-derived factor (SDF)-1 stimulated EPCs mobilization, as demonstrated by Sarto *et al*[112].

Even though the studies mentioned above followed different methodologies and exercise training protocols, we may assume that regular exercise training increases significantly circulating EPC levels, both in healthy subjects (rodents and humans) and in a variety of diseases. The strongest evidence so far in cardiovascular disease emerges from studies in CHF and PAD. More data are needed, however, to confirm the results of these preliminary studies and to investigate the optimum exercise protocol in order to maximize the possible beneficial effects.

Summaries of the long-term exercise training effects on EPCs in animals and healthy subjects as well in disease populations are illustrated in Tables 2 and 3, respectively.

EFFECT OF ACUTE EXERCISE ON EPCs

The effect of a single exercise session on EPC levels has also been investigated. Rehman *et al*[120] have demon-

Table 2 Effects of exercise training on endothelial progenitor cells in animals and healthy subjects

Subjects	*n*	Study group; age	Modality	Exercise prescription	Duration	Results	Limitations	Ref.
Mice	12	Exercise group; Control group	Aerobic	Exercise group: Voluntary running 5100 ± 800 m 7 d a week; Control group: No intervention	28 d	↑ EPCs		[101]
Healthy male	10	Exercise (n = 10) 59 ± 2 yr	Home based aerobic	Walking/jogging 60%-75% predicted peak HR 40-50 min-5-7 sessions per week	3 mo	↑ EPC colonies about 100% from 10 ± 3 to 22 ± 5; ↑ Migratory activity about 50% from 683 ± 96 to 1022 ± 123 RFUs	Non control study	[20]
Healthy male	47	Exercise: Elderly (n = 25) 67.8 ± 3.38 yr, young (n = 22) 26.3 ± 3.15 yr	Aerobic	Treadmill 30 min 3 sessions per week	12 wk	↑Re-endothelialization capacity of EPCs from 15% ± 4% to 36% ± 9%	Non control study	[102]
Healthy male (n = 7), female (n = 13)	20	Interval exercise: Moderate (n = 9), heavy (n = 11)	Aerobic	Ergometer moderate interval (10 s @ 120% peak work rate : 20 s @ 20 W); Heavy interval (30 s @ 120% peak work rate : 60 s @ 20 W), 30-40 min 3 sessions per week	6 wk	No significant change on EPC numbers	Non control study measurements took place 48 h after the last session	[103]
Children	182	Intervention (n = 109), control (n = 73)		Intervention group: PA at school 45 min + endurance training 15 min per school day; Control group: PA at school 45 min 2 school day per week	1 school year	↑ CPCs		[104]

EPC: Endothelial progenitor cell; PA: Physical activity.

strated that exercise can acutely (within 5-10 min after completion of exercise) increase EPCs and CACs in 22 volunteer patients that underwent a symptom-limited treadmill or bicycle exercise test. It has been reported that a modified Bruce treadmill acute exercise protocol can significantly contribute to upregulation of circulating EPCs in healthy subjects[121]. In the same study, the plasma NO levels were also increased and there was a significant linear relationship between the enhanced plasma NO levels and increased number of circulating EPCs activity after acute exercise.

Since that study, researchers have sought to investigate the effect of a single bout of strenuous exercise on late outgrowth endothelial cells (OECs). In a non-controlled study of 11 healthy, physically fit subjects, who followed 1 h of high-intensity (80% of the predicted maximum heart rate) aerobic exercise, the numbers of OEC colonies were doubled 1 h after exercise compared to baseline measurements. The OEC levels returned back to baseline levels 48 h after exercise[122]. In another study[123], it was shown that strenuous exercise at 70% of the individual anaerobic threshold for 4 h could lead to a significant rise in progenitor cells (hematopoietic and EPCs).

In a recent study[124], exercise-induced changes in putative EPC gene expression were associated with thrombin production and the authors suggested that they may be increased by long-term exercise training. Moreover, in a study by Van Craenenbroeck *et al*[125], the authors analyzed the concentration of EPC levels before and immediately after a maximal cardiopulmonary exercise test, showing a significant increase of 50% in EPCs.

The acute effect of different exercise durations and intensities on EPC levels was also studied in healthy individuals[126]. In that study, the authors reported that intensive and moderate aerobic exercise for 30 min but not for 10 min increased circulating levels of EPCs.

Furthermore, the analysis of EPC levels in 68 healthy marathon runners after finishing a marathon race, demonstrated no change compared to baseline levels[127]. Similarly, in a more recent study[128], EPC levels were measured in a group of 10 healthy amateur runners after finishing a marathon and after completing a 1.5-km field test. The researchers observed no change in EPC levels after the marathon, while there was a significant increase after the field test. In addition, Goussetis *et al*[129] showed a significant increase in inflammatory markers, which correlated with a rise in EPCs levels in amateur spartathlon runners (246 km). An interesting finding of this study was also the observation that endothelial cell colonies derived from mobilized EPCs contained significantly more cells 48 h after the race than those obtained in controls and in athletes before the race.

While studying a group of healthy young subjects, a group of healthy old and a group of patients with PAD after an acute exercise session, Shaffer *et al*[130] concluded that young healthy individuals have an increased capacity to mobilize EPCs, as compared with older individuals. Interestingly, patients with PAD appeared to be unable to mount a significant increase in circulating EPCs, despite the ischemic stimulus. Van Craenenbroeck *et al*[131] studied 41 CHF patients (22 mild, 19 severe) and 13 healthy subjects while performing a symptom limited cardiopulmonary exercise test. Even though there was no significant change in circulating $CD34^+$ cells and $CD34^+/KDR^+$

Table 3 Effects of exercise training on endothelial progenitor cells in different disease populations

Subjects	*n*	Study group; age	Disease	Modality	Exercise prescription	Duration	Results	Limitations	Ref.
Mice	12	Exercise; Control	Advanced atherosclerotic lesions; Early atherosclerotic lesions	Aerobic	Voluntary running	8 wk	No change on advanced atherosclerotic lesions; ↑ EPC levels on early atherosclerotic lesions		[107]
Mice	10	Exercise; Control	After traumatic brain injury	Aerobic	Exercise group: Treadmill 22 m/min 30 min 7 d per week; Control group: No intervention	1 wk	↑ Neuronal stem cell		[108]
Male (n = 24); Female (n = 51)	64	Exercise (n = 32); Control (n = 32) 67.1 ± 8.4 yr old	Coronary artery disease	Aerobic + resistance exercise	Exercise group: Bicycle ergometer, treadmill, rowing, steps, arm ergometer + dumbbell, weight training 80% of HRmax 50 min + (5 min warm-up and 5 min cool down) 3 sessions per week	8 wk	No change		[109]
Male (n = 92); Female (n = 20)	112	Exercise (n = 112) 58.2 ± 9.5 yr old	After acute coronary syndrome	Aerobic	Exercise group: Bicycle ergometer 60%-70% of peak VO2 30 min + (5 min warm-up and 5 min cool down) 3 sessions per week	30 d	↑ EPC levels + ↓ pro-inflammatory markers	No controls; No homogeneity of population	[110]
Male (n = 20); Female (n = 10)	30	Exercise (n = 16); Control (n = 14) 67 ± 12 yr old	Hemodialysis	Aerobic	Exercise group: Treadmill/walking 50% max speed 10 min 2 sessions per day; Control group: No intervention	6 mo	No change	Small sample size; No standarized work	[111]
Male (n = 16); Female (n = 6)	22	Exercise (n = 22) 61.4 yr old (SE 1.60)	CHF NYHA Ⅱ or Ⅲ	Aerobic	Exercise group: Bicycle ergometer 60% of HR reserve 45 min + (5 min warm-up and 5 min cool down) 3 sessions per week	8 wk	↑ EPC levels	No controls; No homogeneity of population	[112]
Male (n = 30); Female (n = 8)	38	Exercise (n = 21) 61.3 ± 2.2 yr old; Control (n = 17) 63.4 ± 3 yr old	CHF	Aerobic	Exercise group: 90% HR 60 min 3 sessions per week; Control group: No intervention	6 mo	Improves CAC migratory capacity; ↑ EPC levels	No randomization	[113]
Male (n = 16); Female (n = 12)	28	Exercise (n = 14) 72 ± 11 yr old; Control (n = 14) 73 ± 11 yr old	CHF Exercise NYHA Ⅱ; Control NYHA Ⅰ	Calistenics + aerobic	Exercise group: Bicycle ergometer 75%-85% of HRmax 30 min 2 sessions per day 6 sessions per week; Control group: No intervention	3 wk	↑ EPC levels	Small sample size	[114]
Male	37	Exercise (n = 18) 60 ± 11 yr old; Control (n = 19) 62 ± 10 yr old	NYHA functional class Ⅲb	Aerobic + calisthenics + noncompetitive ball games	Exercise group: Bicycle ergometer in hospital (50% of VO2max 5-20 min, 3-6 sessions per day, 3 wk) home exercise (60% of VO2max 20-30 min, 7 sessions per week, 12 wk) + 1 supervised session (60 min, walking, calisthenics, ball games); Control group: No intervention	12 wk	↑ EPC levels		[115]
Male	37	Exercise (n = 15) 65 ± 7 yr old; CHF control (n = 15) 63 ± 7 yr old; Healthy control (n = 7) 66 ± 4 yr old	NYHA functional class Ⅱ	Aerobic	Exercise group: Bicycle ergometer HR of ventilatory threshold 30 min 5 sessions per week; Control groups: No intervention	3 mo	Exercise group ↑ EPC levels; Control patient group no change		[116]
Male (n = 24); Female (n = 16)	40	Exercise (n = 30) 69 ± 8 yr old; Control (n = 20) 70 ± 11 yr old	PAD	Aerobic	Exercise group: Treadmill intermittent walking 5-10 min warm-up 35-50 min 2 sessions per week; Control group: No exercise intervention	6 mo	↑ EPC levels		[117]
Male (n = 22); Female (n = 18), median age 48 yr	40	Exercise (n = 40); Group A (n = 21) compliant individuals; Group B (n = 19) noncompliant individuals	Overweight and obese BMI ⩾ 25 kg/m²	Aerobic	Non supervised self reported walking briskly or moderate running 45 min HR @ the individual anaerobic threshold 3 sessions per week	3 mo	Group A ↑ EPC levels; Group B no change	Small sample size; Limited duration of follow-up; Non valid compliance measurement; Unable to distinguish which (exercise or weight change) contributed to the increased EPC levels	[118]

EPC: Endothelial progenitor cell; BMI: Body mass index; NYHA: New York Heart Association; CHF: Chronic heart failure; CAC: Circulating angiogenic cell; PAD: Peripheral arterial disease.

Table 4 Acute effects of exercise in healthy subjects

Subjects	*n*	Study group; age (yr)	Modality	Exercise	Results	Limitations	Ref.
Men	22	Healthy 54 ± 10	Symptom limited exercise test	Treadmill/bicycle	↑ EPC + ↑ CAC		[120]
Men	16	Healthy 25.1 ± 2.7	Bruce modified	Treadmill	↑ EPC + ↑ NO level		[121]
Men (*n* = 2); Women (*n* = 9)	11	Healthy 31 ± 16	1 h Spinning session	Bicycle 80% HRmax	↑ OEC	No accurate peak VO2 measurements, no gender differentiation	[122]
Men	18	Healthy (sportive) 32.4 ± 2.3	Ergometer test	Bicycle 70% IAT 240 min	↑ EPC	No control	[123]
Men	23	Endurance athletes 62 ± 1.6; Healthy low active 65 ± 1.5	Exercise test	Treadmill 75% ± 5% VO2max 30 min (5 min ramp-up + 25 min + 3 min cool down)	No change in both groups, no change between groups		[124]
Men; Women	25	Group Ⅰ (*n* = 11) 23.9 ± 1.4; Group Ⅱ (*n* = 14) 36.2 ± 9.3	Symptom limited cardiopulmonary exercise test	Bicycle ergometer: 40 W warm up; 20 W incremental test	↑ EPC	Small sample size	[125]
Men	25	Healthy	Running exercise	Protocol 1 30 min 100% IAT; Protocol 2 30 min 80% IAT; Protocol 3 10 min 80% IAT	Protocol 1 ↑ EPC; Protocol 2 ↑ EPC; Protocol 3 no change		[126]
Men	68	Marathon runners 57 ± 6	Marathon	Race	No change		[127]
Men	10	Marathon protocol (*n* = 9) 43.6 ± 11.6; Field test protocol (*n* = 8) 43.4 ± 10.9	Running exercise	Marathon protocol marathon race; Field test protocol 1500 m max speed	Marathon protocol no change; Field test protocol ↑ EPC		[128]
Men	20	Spartathlon runners (*n* = 10) 42.8 ± 1.4 Control sedentary (*n* = 10) 42.2 ± 10.4	Spartathlon	Exercise group race (246 km); Control group no intervention	Spartathlon runners ↑ EPC; Control no change		[129]

EPC: Endothelial progenitor cell; CAC: Circulating angiogenic cell; IAT: Individual anaerobic threshold.

progenitor cells, an improvement in CAC migratory capacity was most prominent in severe CHF, increased to levels that were no longer different from healthy controls. The same research group just recently sought to investigate whether the above result reflected an attenuated or delayed mobilization of EPCs, so they measured $CD34^+$/KDR^+ EPCs over a longer time period post-graded exercise testing (GXT). Even though the number of subjects was small (7 CHF patients and 8 healthy controls), the authors reported that EPC numbers increased within 10 min following GXT and remained elevated for up to 2 h. In CHF patients, the initial increase was small and normalized within 30 min[132].

From the current literature it emerges that the acute effect of a single exercise session, either performed as an exercise test, or as a single bout of strenuous exercise, can lead to a significant rise in EPCs in healthy subjects. On the contrary, there are still conflicting data with regard to long distance runners (e.g., marathon, spartathlon) and for this reason further investigation is required prior to definite conclusions. In CHF patients it seems that acute exercise might exert a rise in EPCs; however, the small number of studies with different exercise protocols, methodologies and the small number of study participants limit preliminary study results. Further investigational studies targeting on exercise characteristics (modality of exercise, intensity, duration, *etc*.) are also needed to elucidate the acute exercise effects on EPCs in CHF.

Schematic results from the acute effects of exercise in healthy subjects and disease are presented in Tables 4 and 5.

The mechanisms behind the exercise-induced mobilization of EPCs are not fully understood. In patients with cardiovascular disease, exercise-induced ischemia seems to stimulate augmentation of EPCs[133]. In healthy subjects, tissue ischemia is not normally expected to occur due to exercise, but strenuous exercise at levels above what is defined as anaerobic levels, might induce oxidative stress and an inflammatory response and thus could stimulate the release of EPCs from the bone marrow[121,122]. Researchers have hypothesized[34,132] that, in an attempt to address vascular damage, EPCs show a compensatory increase in patients with mild to moderate CHF. Interestingly, VEGF and SDF are potent angiogenic factors that have been shown to increase after exercise sessions with concomitant rise in EPCs in cardiovascular disease, indicating a possible pathophysiological link. Therefore, endothelial factors, cytokines, bone-marrow-derived factors and oxidative stress are involved throughout exercise training and may explain exercise beneficial effects in health and cardiovascular disease.

In conclusion, recent studies provide evidence for the novel concept that physical activity, either performed as a single exercise session or performed as part of an exercise training program, results in a significant increase in circulating EPC levels. Moreover, in patients with cardiovascular disease, exercise training markedly improves vascular endothelium. However, future studies with larger sample sizes are required to investigate and confirm possible exercise training-induced EPCs rise in both healthy subjects and specific subsets, such as patients with hypertension, obesity, OSA, dyslipidemia, diabetes, CAD, PAD, or CHF. Studies should aim to characterize the optimum

Table 5 Acute effects of exercise in different disease populations

Subjects	*n*	Study group; age (yr)	Disease	Modality	Exercise prescription	Duration	Results	Ref.
Men	37	Young group (n = 9), mean age 33; Old group (n = 13), mean age 66; PAD group (n = 15), mean age 69	PAD	Treadmill	Young group bruce protocol; Old group gardner protocol; PAD group gardner protocol	Young group until exhaustion or 15 min; Old group 10 min; PAD group symptom limited or 10 min	Young group ↑ EPCs; Old group no change; PAD group no change	[130]
Male (n = 41); Female (n = 13)	54	Healthy controls (n = 13) 55.7 ± 1.6; Mild CHF (n = 22) 61.9 ± 2.5; Severe CHF (n = 19) 63 ± 2.6	CHF	Bicycle ergometer	Cardiopulmonary exercise testing individualized ramp protocol	8-10 min	EPC no change; Improved CAC migration in mild CHF + severe CHF	[131]
Male (n = 13); Female (n = 2)	15	Young group (n = 4) mean age 33; Old group (n = 4) mean age 66; CHF group (n = 7) mean age 69	CHF Ⅱ / Ⅲ	Bicycle ergometer	Symptom-limited graded exercise test		↑EPCs in young group; ↑EPCs in old group; Non significant ↑EPCs in CHF group	[132]

EPC: Endothelial progenitor cell; CHF: Chronic heart failure; CAC: Circulating angiogenic cell; PAD: Peripheral arterial disease.

exercise regimen with regard to type, intensity and duration of exercise that may increase EPC levels. Confirming evidence will give the opportunity to the medical community to use a non-pharmacologic intervention, such as exercise, to mobilize EPCs. Revealing the mechanisms of exercise-induced EPC mobilization may result in the development of optimum exercise protocols to improve endothelial function and enhance angiogenesis.

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REVIEW

Blood pressure, prevalence of hypertension and hypertension related complications in Nigerian Africans: A review

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Abstract

To review studies on hypertension in Nigeria over the past five decades in terms of prevalence, awareness and treatment and complications. Following our search on Pubmed, African Journals Online and the World Health Organization Global cardiovascular infobase, 1060 related references were identified out of which 43 were found to be relevant for this review. The overall prevalence of hypertension in Nigeria ranges from 8%-46.4% depending on the study target population, type of measurement and cut-off value used for defining hypertension. The prevalence is similar in men and women (7.9%-50.2% *vs* 3.5%-68.8%, respectively) and in the urban (8.1%-42.0%) and rural setting (13.5%-46.4%). The pooled prevalence increased from 8.6% from the only study during the period from 1970-1979 to 22.5% (2000-2011). Awareness, treatment and control of hypertension were generally low with attendant high burden of hypertension related complications. In order to improve outcomes of cardiovascular disease in Africans, public health education to improve awareness of hypertension is required. Further epidemiological studies on hypertension are required to adequately understand and characterize the impact of hypertension in society.

Key words: Blood pressure; Hypertension; Prevalence; Non-communicable disease; Nigeria

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INTRODUCTION

Hypertension is a common, important and major global public health problem[1].

Its prevalence has been found to be 44% in Western Europe and 28% in North America. It has been documented as a threat to the health of people in sub-Saharan Africa and a major contributor to morbidity and mortality in the sub-region[2-4]. There is emerging evidence to show that the pattern of diseases in sub-Saharan Africa is changing, with non-communicable diseases (NCD) responsible for about 22% of the total deaths in the region in 2000, cardiovascular disease alone accounting for 9.2% of the total mortality [World Health Organization (WHO) 2002]. According to Kearney *et al*[5], by 2025 about 75% of the world hypertensive population will be in developing countries. In Nigeria for example, it is the number one risk factor for stroke, heart failure, ischemic heart disease, and kidney failure. With an increasing adult population as well as rising prevalence of hypertension, Nigeria will experience economic and health challenges due to the disease if the tide is not arrested. As far back as the early 60s a lot of interest has been shown by workers on the blood pressure of Nigerian Africans. The essence of this work is to review studies on hypertension as well as hypertension research in the country.

COUNTRY PROFILE

Nigeria is classified as a low-middle income country with a Gini Index of 43.7 and income per capita of $1490. 49% of the population is living in urban areas, the gross national income per capita is $2070. Life expectancy at birth is 51 years for both sexes (53 for men and 54 for women).The probability of dying between 15 and 60 years for men and women (per 1000 population) is 377 and 365 respectively. The mortality rate for under 5s is 138/1000 and the maternal mortality ratio is 840/10^5 live births. Non-communicable diseases contribute about 14% of the number of years of life lost. The number of doctors/10 000 population is about 4. Five point one percents of men and 9.0% of women aged 20 years and above are obese; 11.9% of men and 1.0% of women aged 15 years and above smoke cigarettes.

The prevalence of HIV (per 1000 adults aged 15-49 years) is 36 while the prevalence of tuberculosis (per 100 000 population) is 497[6-8].

METHODS

The Pubmed scientific database was searched from 1950-2011 for studies of blood pressure and hypertension in the country. The search criteria were "Hypertension", "High Blood Pressure" and "Nigeria". Studies conducted mainly on adult subjects were included.

Additional references were sought from retrieved publications. The African index medicus, African Journal Online and WHO Global cardiovascular infobase were also searched.

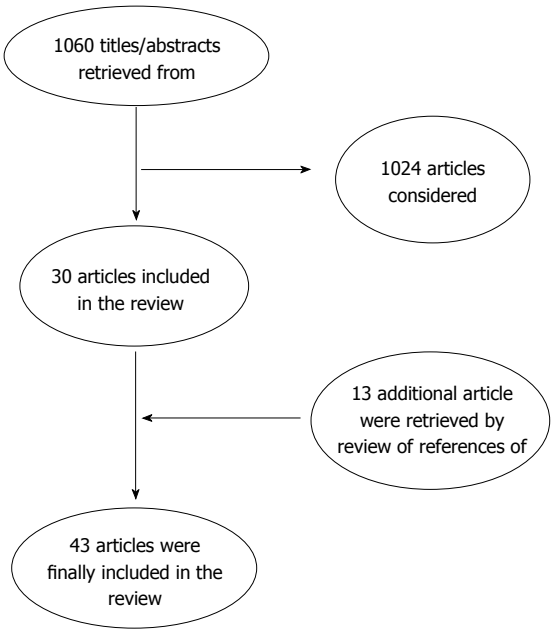

Figure 1 Selection process.

All the data collected were entered into an excel spreadsheet. Information collected include: first author's name, year of publication, place of study, study design, population, sample size, mean age range, proportion of women enrolled, mean age, and prevalence of hypertension in the sample population as well as in men and women.

The pooled prevalence rate of hypertension was computed for the period 1970-1979, 1990-1999, and 2000-2011 from community-based studies.

RESULTS

Our search yielded a total of 1060 references. However 30 publications were found to be useful for this review. An additional 13 articles were retrieved through the review of the bibliography of the earlier obtained articles. Figure 1 is a summary of the selection process. These cross-sectional studies were published between 1960 and 2012 in 12 of the 36 states of Nigeria: Oyo[9-22], Enugu[23-27], Lagos[28,29], Osun[30,31], Edo[32-35], Cross-River[36,37], Akwa-Ibom[37], Rivers[38], Kastina[39], Sokoto[40], Borno[41] and Abia[42]. Three of the studies involved more than one state[37,43].

In terms of geopolitical spread, the majority of studies were conducted in the Southwestern part of the country; some of the studies were conducted before 1990 while the majority were after 1990.

Historical vignette

Many years ago it was generally believed that high blood pressure was rare in native Africans. This was based on reports mainly by workers on the eastern coast of the continent such as Cooke[44], Donnison[45], Jex-Blake[46] and Vint[47].

The earliest report of hypertension in Nigerian Africans was probably by Callander[48]. He commented on the blood pressure of army recruits and Nigerian soldiers at routine medical examination. He noted that in 100 healthy soldiers, 52 had a systolic blood pressure > 140 mmHg, and 23 had a diastolic blood pressure (BP) > 90 mmHg.

His observations from the army recruits were more remarkable. In 400 recruits aged between 19-24 years, 42.5% were rejected on account of elevated blood pressure and "this after an hour's rest and amytal sedation before the pressure was recorded".

In two reports in 1956, hypertension was documented as a cause of cardiovascular disease in Nigerians.

Beet *et al*[49] noted that it was responsible for 34% of cases of heart failure in Northern Nigeria while Nwokolo *et al*[50] also documented some cases in Enugu in the Eastern part of the country. Also Lambo *et al*[51] reported on the association of high blood pressure and mental disorder in elderly psychiatric patients in the Western region.

The earliest and first large scale study of blood pressure in Nigerians was by Abrahams *et al*[11]. The study was conducted in a rural town of Ilora which is about 50 km north of Ibadan. They noted, like most other studies conducted during that period, in Caucasians and American Blacks that blood pressure rose with age in both men and women. However, they did not document any clear relationship between blood pressure, weight climate and diet. This was followed by studies by Smith[28] in Lagos, Akinkugbe *et al*[9] in Ibadan, Johnson[52] in Lagos, Oviasu *et al*[32-35] in Benin city and Oyediran in Epe near Lagos.

Akinkugbe is generally regarded as the father and doyen of blood pressure and hypertension research in Nigeria because of his seminal work in this field in the late 60s and 70s[9,10,53-62]. He documented that: (1) Systolic blood pressure rose with age in both sexes and in all age groups from 12-70 years. This trend was less marked in diastolic blood pressure; (2) Blood pressure levels were similar in women from rural and urban areas but seemed much higher in urban than in rural men; (3) The rate of rise of pressure was more rapid in earlier decades than subsequently; (4) There was little correlation with weight and much less so with height after 40 years of age; (5) The incidence of proteinuria was highest in the early teenage group years, but did not relate to blood pressure trends; and (6) Casual systolic and diastolic pressure differed in no important respects from those in Negro populations in the Caribbean, but systolic and diastolic values are marginally higher in United States Negroes than in West Indian or West African Negroes".

Cole *et al*[63] was the first to conduct a drug trial on hypertensive patients and this was followed by a series of work by Salako *et al*[64-69]. Falase *et al*[70-72] demonstrated the lack of effect of low doses of prazosin in the treatment of hypertension in Nigeria.

A series of studies by Salako and Falase showed that Nigerians responded well to thiazide diuretics and calcium channel antagonists when these drugs were used as monotherapy. Other classes of drugs, such as beta adrenergic blockers, require the use of high doses before they are effective in Nigerian hypertensives. The use of high doses of these drugs often causes unacceptable side effects. These classes of antihypertensive drugs are, however, effective in low doses when they are combined with either thiazide diuretics or calcium channel antagonists or both. Effective management of hypertension in Nigerians therefore requires the use of thiazide diuretics or calcium channel antagonists as monotherapy or in combination with other classes of antihypertensive agents.

Osuntokun *et al*[73-76] first studied hypertension in diabetic subjects in the country and showed in many seminal research studies the contribution of hypertension as a risk factor for stroke in hospital based and population based studies. Akerele documented hypertension in Nigerian children in 1974. The relation of renal disease, hypertension and schistosomiasis was explored by Soyannwo *et al*[77-81].

Table 1 shows the hypertension research from 1961-1981.

Diagnosis of hypertension

Earlier studies used 160/95 mmHg as the benchmark for the diagnosis of hypertension. The vast majority of studies which were conducted in the last 20 years used 140/90 mmHg as the cut off.

Twenty of the studies were carried out in urban populations, 11 in rural communities, while the remaining 6 were conducted both in urban and rural populations. The majority of the population based studies used multistage cluster sampling.

Sampling in five of the studies was by convenience (during free medical programmes).

The sample size in the studies ranged from 132 to 4930 subjects. The proportion of women who participated ranged from 24.9% to 71.2% while the mean age of the population ranged from 31.6 years to 61.2 years.

Prevalence of hypertension

The prevalence of hypertension in both men and women ranged from 8% to 46.4%; with regards to gender, the prevalence of hypertension ranged from 7.9% to 50.2% and 3.5% to 6.8.8% in men and women, respectively. The reported prevalence in rural areas ranged from 13.5%-46.4% in both sexes, 14.7%-49.5% in men and 14.3-68.8% in women. Data from urban studies revealed a range of 8.1%-42.0% in both men and women, 7.9%-46.3% for men and 3.5%-37.7% for women. In general hypertension prevalence was higher in urban than rural areas (Table 2).

Pooled prevalence and trend: A prevalence of 8.9% was estimated from the only community-based study available for 1970-1979. For 1990-1999, the pooled prevalence of hypertension was 15.0% (CI 13.7-16.3). The pooled prevalence increased significantly to 22.5% (CI 21.8-23.2) from 2000 to 2009.

Table 1 Events in the first 21 years of blood pressure and hypertension research in Nigeria (1961-1981)

No.	Author	Year	Comments
1	Abrahams *et al*[11]	1961	First population based study of blood pressure in the country. Studied the systemic blood pressure of rural Nigerians resident in Ilora
2	Monekosso[82]	1964	Reported some cases in a clinical survey of a village in South West Nigeria
3	Smith[28]	1966	Studied blood pressure of urban inhabitants in Lagos
4	Akinkugbe[56]	1968	Documented the rarity of hypertensive retinopathy in Nigerians
5	Akinkugbe *et al*[57]	1968	Reported on the rarer causes of hypertension in Nigeria
6	Akinkugbe *et al*[9]	1968	Wrote on arterial blood pressure in rural Nigerians in Eruwa
7	Akinkugbe[58]	1969	Reported on the hypertensives diseases in Ibadan , Nigeria
8	Akinkugbe[60]	1969	Wrote on antihypertensive therapy in the African context
9	Ojo *et al*[83]	1969	Studied hypertension in pregnancy
10	Akinkugbe[59]	1969	Reported on the result of his survey of blood pressures in school children
11	Cole *et al*[63]	1970	First documented drug trial (Declinax) in hypertensive Nigerians
12	Brockington[84]	1971	Reported on postpartum hypertensive heart failure
13	Johnson[52]	1971	Reported on his study of blood pressure in rural areas around Lagos
14	Carlisle[85]	1971	Reported on the remission of hypertension in some Nigerians
15	Salako[64]	1971	First trial of oral thiazides
16	Salako[65]	1971	Reported on serum electrolytes in hypertensive Nigerians
17	Salako[66]	1972	Reported on electrolyte changes following thiazide therapy in hypertensive Nigerians
18	Osuntokun *et al*[73,74]	1972	Seminal work on hypertension in diabetic Nigerians
19	Salako *et al*[67]	1973	Evaluated the usefulness of Moduretic in the treatment of hypertension in Nigerians
20	Akinkugbe *et al*[61]	1974	Reported on the experience with beta blockers in hypertension management
21	Aderele[86]	1974	Documented on hypertension in Nigerian children
22	Akinkugbe[87]	1976	Studied blood pressure in non-pregnant women
23	Falase *et al*[70]	1976	Demonstrated lack of effect of low dose prazosin in hypertensive Nigerians
24	Etta *et al*[88]	1976	Assessed the relation of blood pressure to indices of obesity
25	Olatunbosun *et al*[89]	1976	Evaluated the relation of blood pressure to heavy metals
26	Jain *et al*[90]	1977	Reported on the incidence of hypertension in Abuth Zaria
27	Akinkugbe *et al*[62]	1977	Conducted a biracial study of blood pressure in school children
28	Olatunde *et al*[91]	1977	Trial of beta blockers in hypertensive Nigerians
29	Osuntokun *et al*[75,76]	1977	Demonstrated through hospital registry and population based studies that hypertension is a major risk factor for stroke in Nigeria
30	Abdurrahman *et al*[92]	1978	Studied blood pressure in school children in Northern Nigeria
31	Mabadeje[93]	1979	Conducted a trial of chlorthalidone in hypertensive Nigerians
32	Falase *et al*[71,72]	1979	Documented poor response of hypertensive Nigerians to Beta blockers monotherapy
33	Alakija[94]	1979	Pilot study of hypertension in Benin City
34	Abengowe *et al*[95]	1980	Reported on the pattern of hypertension in Northern Savannah
35	Oviasu *et al*[32-35]	1980	Document on blood pressure and hypertension in urban city of Benin/ Occupational factors in hypertension
36	Ladipo[96]	1981	Carried out a study on hypertensive retinopathy in Ile-Ife

Impact of blood pressure cut-off threshold on the prevalence of hypertension: In a study of the prevalence and patterns of hypertension in a semi-urban community in South Western Nigeria, Adedoyin *et al*[31] demonstrated that with a cut-off value of ⩾ 140/90 mmHg for the diagnosis of hypertension, the prevalence was 36.6% (isolated systolic hypertension (ISH) in 22.1% and isolated diastolic hypertension (IDH) in 14.5%).

On the other hand when the threshold was increased to 160/95 mmHg, only 13.35% were found to be hypertensive (6.63% had both ISH and IDH).

A male:female ratio of 1.7:1 and 1:5 was documented for blood pressure of ⩾ 140/90 mmHg and ⩾ 160/90 mmHg, respectively.

Impact of age: In all the studies, the most likely determinant of blood pressure and presence of high blood pressure was age. BP was shown to increase steadily with age from the youngest to the oldest age brackets, irrespective of gender.

It appears that population mean blood pressure has increased over the years since the first survey by Abrahams *et al*[11]. This may be due to an increase in detection rather than a temporal increase as the observation is limited by a lack of serially conducted studies in any of the populations.

Comparison of prevalence of hypertension in Nigeria with some other parts of Sub-Saharan Africa: Figure 2 shows the comparison of prevalence of hypertension in different parts of Sub-Saharan Africa, including Nigeria, as estimated for 2008 by Twagirumukiza *et al*[97]. The overall prevalence of hypertension was put at 18.4% for Nigeria compared with a prevalence of 10.35% for Ethiopia and 23.0% for Ghana (Figure 3).

Hypertension awareness, treatment and control

As in many populations of the world, the awareness of hypertension is low in Nigeria. In four of the studies, the reported awareness rates were 14.2% in rural areas by Oladapo *et al*[22], 18.5% in Edo State[98], and 29.4% and 30.0% in semi-urban and urban populations in Enugu State[25,26].

The proportion of hypertensives on treatment was reported to be 21% (23.7% men, 17.5% women) by Ekwunife *et al*[99] and 18.6% (19.0% men, 18.4% women) by Oladapo *et al*[22].

Table 2 Prevalence of hypertension in 38 studies in Nigeria (1960-2011)

No.	First author	Year	Study location	State	Region	BP cut off	Target population	Setting	Sample size	% all	% men	% women
1	Abrahams *et al*[11]	1960	Ilora	Oyo	SW	160/90	Community based	Rural	457	13.3	NA	NA
2	Smith[28]	1961	Lagos	Lagos	SW	160/95	Hospital based	Urban	207	8.8	9.5	7.9
3	Akinkugbe *et al*[9,10]	1968	Eruwa	Oyo	SW	140/90	Community based	Rural	3602	10.1	9.1	11.2
4	Johnson[52]	1971	Lagos	Lagos	SW	160/95	Community based	Urban	1392	8.9	7.9	9.9
5	Jain *et al*[90]	1977	Kaduna	Kaduna	NW	160/95	Hospital based	Urban	2950	3.8	2.9	4.9
6	Oviasu *et al*[32,33]	1978	Isi-uwa	Edo	SS	160/100	Community based	Rural	1482	2.1	2.8	0.5
7	Oviasu *et al*[34,35]	1980	Benin city	Edo	SS	140/90	Civil servants	Urban	1265	13.3	14	10
8	Idahosa[110]	1987	Benin city	Edo	SS	140/90	Civil servants	Urban	1450	15.1	NA	NA
9	Ogunlesi *et al*[12]	1991	Ibadan	Oyo	SW	160/95	Male factory workers	Urban	541	8		
10	Ekpo *et al*[36]	1992	Calabar	Cross river	SS	160/95	Civil servants, factory workers, plantain workers	Urban	4382	8.1	8.9	3.5
11	Bunker *et al*[111]	1992	Benin city	Edo	SS	140/90	Civil servants	Urban	559	20-43	21.6	12.5
12	Kaufman *et al*[16]	1996	Ibadan	Eyo	SW	140/90	Community based	Urban	205	11		
13	Kaufman *et al*[17]	1996	Ibadan	Oyo	SW	140/90 (160/95)	Rural farmers/urban poor/retired railway workers	Rural/urban	598	14,25,29 (3,11,14)	-	-
14	Cooper *et al*[112]	1997	National	National	National	140/90	Community based	Rural	2509	14.5	14.7	14.3
15	Akinkugbe[113]	1997	National	National	National	160/95	Community based	Rural/urban	4930	10.7		
16	Owoaje *et al*[14]	1997	Ibadan	Oyo	SW	140/90	Community based	Urban	247	23.4	22.2	24.3
17	Kadiri *et al*[114]	1999	Ibadan	Oyo	SW	160/95	Civil servants	Urban	917	9.3	9.8	8
18	Olatunbosun *et al*[13]	2000	Ibadan	Oyo	SW	160/95	Civil servants	Urban	998	10.3	13.9	5.3
19	Lawoyin *et al*[20]	2002	Ibadan	Oyo	SW	140/90	Community cohort	Urban	2144	12.4	12.1	12.7
20	Onyemelukwe[115]	2003	Lagos	Lagos	SW	140/90	Community based	Rural/urban	1082	SHT 22.5, DHT 24.7	NA	NA
21	Akinkugbe[116]	2003	Lagos	Lagos	SW	140/90	Community based	Rural/urban	1018	34.8	36.2	33.5
22	Erhun *et al*[117]	2005	Ile-ife	Osun	SW	140/90	University community	Urban	1000	21	23.3	16.4
23	Oghagbon *et al*[118]	2008	Ilorin	Kwara	NC	140/90	Factory workers	Urban	281	27.1	28.4	22.9
24	Omuemu *et al*[98]	2007	Udo	Edo	SS	140/90	Community based	Rural	590	20.2	26.2	13.2
25	Ukoh[119]	2007	Benin city	Edo	SS	140/90	Hospital based	Urban	2852	20.2	NA	NA
26	Nwankwo *et al*[41]	2008	Maiduguri	Borno	NE	140/90	Community based	Rural/urban	224	40 (urban), 27.8 (rural)		
27	Adedoyin *et al*[31]	2008	Ile-ife	Osun	SW	140/90	Community based	Rural	2250	18.7	15.5	21
28	Ekore *et al*[21]	2009	Ibadan	Oyo	SW	140/90	Hospital based	Urban	405	30.6	34.4	28.2
29	Ulasi *et al*[26]	2010	Njodo Nike, Enugu	Enugu	SE	140/90	Community based	Semi-urban/rural	1939	35.4 (urban), 25.1 (rural)	NA	NA
30	Ekwunife *et al*[99]	2010	Nsukka	Enugu	SE	140/90	Community based	Urban	756	30	40.3	24.7
31	Sani *et al*[39]	2010	Katsina	Katsina	NW	140/90	Hospital based	Urban	300	25.7	27.9	24
32	Adegoke *et al*[30]	2010	Ile-ife	Osun	SW	140/90	Community based	Rural	132			
33	Oladapo *et al*[22]	2010	Egbeda	Oyo	SW	140/90	Community based	Rural	2000	20.8	21.1	20.5
34	Ahaneku *et al*[27]	2011	NA	Enugu	SE	140/90	Community based	Rural	218	44.5	49.5	42.3
35	Onwubere *et al*[24]	2011	Ezeagu	Enugu	SE	140/90	Community based	Rural	858	46.4	31.2	68.8
36	Ejim *et al*[23]	2011	Imezi owa,	Enugu	SE	140/90	Community based	Rural (middle age/elderly)	858		50.2	44.8
37	Ulasi *et al*[25]	2011	Enugu	Enugu	SE	140/90	Traders	Urban	731	42	46.3	37.7
38	Hendriks *et al*[120]	2011	Afon and Ajasse Ipo	Kwara	NC	140/90	Community based	Rural	2678	19.3	NA	NA
39	Isezuo *et al*[40]	2011	Sokoto	Sokoto	NW	140/90	Community based	Rural	782	24.8	25.9	23.6
40	Andy *et al*[37]	2012	CRS/AK	CRS/AK	SS	140/90	Community Based	Rural	3869	23.6	31.2	18.1
41	Onwuchekwa *et al*[38]	2012	Kegbara-Dere	Rivers	SS	140/90	Community based	Rural	1078	18.3	-	-
42	Odugbemi *et al*[121]	2012	Lagos	Lagos	SW	140/90	Traders	Urban	400	34.8	-	-
43	Ogah *et al*[42]	2012	Abia	Abia	SE	140/90	Community	Rural/urban	2983	SHT 31.4, DHT 22.5	Rural: SHT 33.5, DHT 23.4; Urban: SHT 33.6, DHT 20.6	Rural: SHT 30.5, DHT 25.4; Urban: SHT 26.4, DHT 18.4

SW: South west; SE: South east; SS: South south; NW: North west; NE: North east; NC: North central; NA: Not available; SHT: Systolic hypertension; DHT: Diastolic hypertension; BP: Blood pressure.

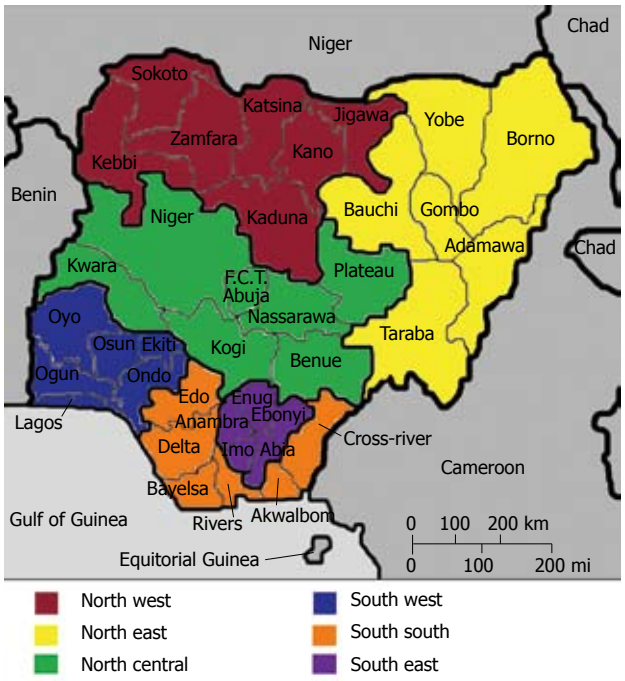

Figure 2 Map of Nigeria showing the 36 states and federal capital territory as well as the 6 geopolitical zones.

Blood pressure control was poor; it was reported as 9% (5% in men and 17.5% in women) by Ekwunife *et al*[99].

Studies on pathophysiology of hypertension in Nigeria

Osotimehin *et al*[100] estimated plasma Na+-K+ ATPase inhibitor by a technique in which it competes with ouabain for binding on red cells in normotensives without a family history of hypertension, normotensives with a family history of hypertension and hypertensive individuals. They observed that plasma levels of the inhibitor were significantly higher in the last two groups and that this correlated positively with urinary sodium excretion in the three groups.

In another study, the author demonstrated low renin activity in hypertensive Nigerians[101].

Ogunlesi *et al*[102] and Aderounmu *et al*[103] studied intracellular sodium and blood pressure and showed that erythrocyte sodium (ENa) was higher in hypertensives compared with normal controls. ENa also correlated with systolic and diastolic blood pressure. Obasohan *et al*[104] went further to demonstrate higher sodium-lithium counter-transport (SLC) activity and ENa levels both in hypertensive subjects and their offspring.

In a more recent study, Adebiyi *et al*[105] showed that plasma noradrenaline level was higher in hypertensive subjects compared to control subjects. Hypertensive Nigerians also have lower levels of plasma renin, angiotensin converting enzyme (ACE) and atrial natriuretic peptide (ANP). Systolic blood pressure positively correlated with plasma noradrenaline but negatively with renin, ACE and ANP. This finding of high noradrenaline levels in hypertensive Nigerians supports the hypothesis that activation of the sympatho-adrenergic system might play a dominant role in the pathophysiology of hypertension in Nigerians.

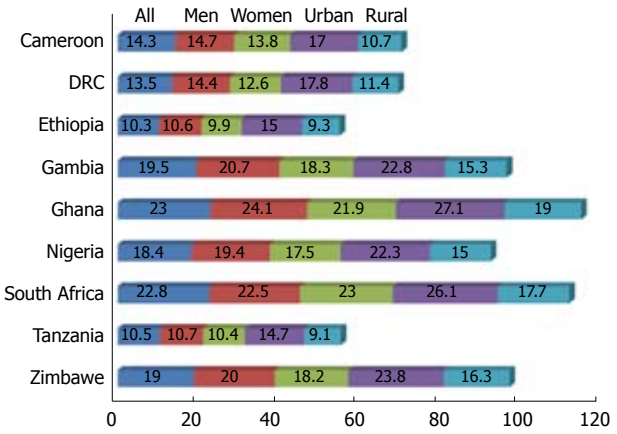

Figure 3 Comparision with other countries.

Several workers have also demonstrated higher salt taste and salt taste threshold in hypertensive individuals as well as their offspring compared to their normotensive counterparts[106-108].

However such a relationship was not demonstrated in adolescent school children[109].

Hypertension related admissions in Nigeria

In a review of the prevalence of hypertension and its complications among medical admissions in Enugu, South Eastern Nigeria, 18% (1360 subjects out of the 7399 admissions in the period between December 1998 and November 2003) had hypertension related diseases. Hypertensive congestive cardiac failure accounted for 26.5% of cases and 46.1% of hypertension related complications. Hypertension with its complications accounted for more than two-thirds (69.6%) of the cardiovascular system admissions[122,123].

In a three year review of adult hypertensive admissions in Benin city (South-South Nigeria), Ukoh[119] reported that 575 out of the total of 2852 adult medical admissions in Benin were as a result of high blood pressure related morbidities. The most common hypertensive complications were stroke, congestive cardiac failure and chronic kidney failure.

In another report from the same region, stroke was the commonest cause of death at the medical emergency room of the University of Portharcourt teaching hospital[124].

In a review of 424 hypertension related admissions in the same hospital (173 males and 251 females, aged 18-100 years with a mean of 56.5 ± 16.2); stroke was responsible for 169 (39.9%) hypertensive complications. "Heart failure occurred in 97 (22%) cases while renal failure and encephalopathy accounted for 40 (9.4%) and 7 (1.7%) hypertensive complications, respectively. There were 99 deaths out of which 51 (51.5%) were due to stroke, 14 (14.12%) were due to heart failure, and 12 (12.1%) were due to renal failure"[125].

During the same period, 191 of the hypertension

related admissions died giving a case fatality of 42.9%. Eighty six (45%) of the deaths occurred during acute hypertensive crises such as stroke, hypertensive encephalopathy and acute renal failure. Other important complications leading to death included heart failure (17.3%) and renal failure (16.8%)[125].

High blood pressure also contributed to the burden of adult medical admissions in Uyo (Southern Nigeria): hypertension related heart failure, stroke or severe uncontrolled hypertension. This was shown to be commoner in the wet seasons of the year[126].

In Sokoto (Northwestern Nigeria), Isezuo *et al*[127] documented hypertension related admissions in 440 subjects admitted in a tertiary centre between 1995 and 2000. Hypertension related morbidities included heart failure (36.4%), stroke (34.8%) and chronic renal failure in 7.1% and other conditions in 21.7%. Hospital admissions for hypertension related morbidities were more generally higher in the rainy season than the dry season.

Kolo *et al*[128] studied hypertension related admissions and outcomes in a tertiary hospital in Bauchi (North Eastern Nigeria). They documented that out of the 3108 admissions into the medical ward of the hospital, 735 (23.7% were related to hypertension with an excess mortality of 42.9%. Stroke was the commonest complication, accounting for 44.4% of cases and had the highest mortality (39.3%). This was followed by chronic kidney disease (36.6%), hypertensive emergencies (30.9%) and heart failure which had the least intrahospital mortality of 27.5%.

Hypertensive target organ damage in Nigeria

Hypertensive target organ damage (TOD) is common in Nigeria. Because of low awareness of hypertension in the country, hypertensive TOD is often what brings patients to healthcare facilities.

Oladapo *et al*[129] recently reported the results of the study of the prevalence and pattern of TOD and associated clinical conditions in 415 hypertensive individuals in a rural community in Southwestern Nigeria. 179 (43.1%) of the participants had evidence of TOD and 45 (10.8%) had established cardiovascular disease. Left ventricular hypertrophy (LVH) was present in 27.9%, atrial fibrillation in 16.4%, microalbuminuria in 12.3% and overt proteinuria in 15.3%.

Furthermore stroke was present in 6.3%, heart failure in 4.6%, retinopathy in 2.2%, ischaemic heart disease in 1.7% and peripheral vascular disease in 3.6%. TOD was significantly higher in those with severe hypertension and diabetes mellitus. In a related study but in younger subjects aged 18-44 years, Ekore *et al*[21] examined 124 individuals for TOD. LVH was present in 22 (17.7%), chronic cardiac failure in 3 (2.4%), retinopathy in 5 (4.0%), nephropathy in 12 (26.1%) and transient ischaemic attacks in one patient (0.8%)

Ayodele *et al*[130] examined 203 patients in an outpatient clinic in Abeokuta and documented LVH in 31%, heart failure in 10.8%, chronic kidney disease (CKD) in 18.2% and stroke in 8.9%.

Hypertensive heart disease

Various aspects of hypertensive heart disease (HHD) have been studied in the country - such as LVH, LV geometry, left atrial structure, function and dysfunction, LV diastolic function and dysfunction, LV systolic function and right ventricular function. The burden of arrhythmias and conduction abnormalities has also been reported in compensated and asymptomatic hypertensives in the country.

Left ventricular hypertrophy: The prevalence of ECG LVH in hypertensive subjects varies from 18%-56% depending on the criteria used. Sokolow-Lyon-Rappaport voltage criteria have the best sensitivity (80%) and area under the receiver operating characteristic curve. Romhilt-Estes score was reported to have the best specificity[131].

In another Nkado *et al*[132] noted a significant correlation of ECG voltage with echocardiographically determined LV mass.

ECG LVH with strain pattern has also been shown to have a worse LV structure and systolic function in hypertensive Nigerians[133].

Left ventricular diastolic dysfunction: LV diastolic dysfunction has been demonstrated in hypertensive Nigerians by various workers[134-138]. Furthermore it has also been demonstrated in offspring of hypertensive individuals. Adamu *et al*[137] reported LV diastolic dysfunction in 62% of hypertensive subjects compared to 11.3% in age and sex-matched controls. Impaired relaxation was the commonest LV filling pattern.

Adebayo *et al*[139] demonstrated early diastolic dysfunction in hypertensives using a newer method of evaluation (tissue doppler imaging). In another study, the authors evaluated left atrial structural and functional alterations in hypertension which was found to be statistically different compared to age and sex-matched apparently normal individuals[140].

LV systolic dysfunction: In a study of 832 unselected hypertensive subjects, Ogah *et al*[141] documented LV systolic dysfunction (LVSD) in 18.1% of the participants (mild LVSD = 9.6%, moderate LVSD = 3.7% and severe LVSD = 4.8%).

LV mass, body mass index and male gender were found to be independent predictors of LVSD in the study.

The Tei index (index of global myocardial performance) was found to be significantly higher in hypertensives compared to controls. This index also increased with severity of hypertensive heart failure. It was found to be inversely related to LV ejection fraction and directly related to some indexes of diastolic function such as E/A ratio and deceleration time[142].

Echocardiographic LVH and LV geometric patterns: Adebiyi *et al*[143] studied the prevalence and pattern

of LVH in a large population of hypertensive Nigerians seen at the University College Hospital, Ibadan. The prevalence of LVH ranged from 30.9%-56.0% depending on the method of indexation employed.

Abnormal LV geometry was documented in 61.1%-74.0% and was commoner in the female gender.

Correlates of LV mass in hypertensive Nigerians: Ogah *et al*[144] assessed the correlates and determinants of LV mass in 285 hypertensive individuals. The authors found that diastolic blood pressure, family history of hypertension, alcohol consumption, left atrial size; LV wall stress and tension were the independent predictors of LV mass (LVM) in these hypertensive subjects.

Right ventricular function and dysfunction: Karaye *et al*[145] reported right ventricular diastolic dysfunction (RVDD) and right ventricular systolic dysfunction (RVSD) in 61.7% and 32%, respectively, of 128 individuals with high blood pressure in Kano. RVSD was highest in those with eccentric LVH. Age was found to be the only determinant of RVDD while LV ejection fraction was a predictor of RVSD after adjusting for confounding variables. In a similar study, Akintunde *et al*[146] reported RV structural and functional alteration in hypertension and concluded that RVDD may be an early precursor of HHD in Nigerians.

The burden of arrhythmias in hypertensive Nigerians: Hypertension and LVH are both risk factors for atrial fibrillation and ventricular arrhythmias.

Okeahialam *et al*[147] studied 1547 ECG tracings obtained from well compensated hypertensive patients over a 5-year period in Jos to determine the burden of arrhythmias. About 10% of patients had one form of arrhythmia or another. The common arrhythmias were ventricular ectopic (133, 86.9%) atrial ectopic (21, 13.7%) and atrial fibrillation (10, 6.5%). Others included sinus arrhythmia in 3 (1.9%), sinus escape beats in 3 (1.9%), wandering pacemaker in 3 (1.9%) and Wolf Parkinson White in 1 (0.7%). Factors associated with the presence of arrhythmias include: age, presence of ECG LVH and left atrial enlargement.

Conduction abnormalities: In the same study, Okeahialam *et al*[147] noted the following conduction abnormalities in 1547 well compensated hypertensive patients. First degree AV block was present in 7 while 6 subjects had right bundle branch block and left bundle branch block.

Hypertension as a risk factor for heart failure in Nigeria: Hypertension is by far the commonest risk factor for congestive heart failure in Nigeria. In the Abeokuta heart failure (HF) registry, hypertension was responsible for 78.7% of HF in the city. It was also responsible for 62.6%, 56.3%, 57% and 44.1% of heart failure cases in Abuja[148], Port Harcourt[149], Jos[150] and Uyo[126] respectively. In the recently published transnational study of HF in sub-Saharan Africa, hypertension was clearly shown as the predominant cause of HF in the region, especially in Nigeria. Ogah *et al*[151] recently described the characteristics of 197 subjects with hypertensive HF in the Abeokuta HF registry. The mean age of the subjects was 58.4 years which is 15-20 years younger than the mean age of patients with HF in the developed world. The male to female ratio was 1.4:1. HF in hypertensive Nigerians was characterized by severe LV systolic dysfunction (65.5%) and abnormal LV geometry (concentric and eccentric LVH). Intrahospital mortality was 3.6%.

It has also been noted that most of the patients diagnosed as having dilated cardiomyopathy in Nigeria are cases of hypertensive heart failure with poor myocardial failure because of poor or no control[152,153].

Hypertension as a major risk factor for stroke in Nigeria

Stroke is currently a major public health problem in Nigeria. As in many developing countries of the world it has some peculiarities. It occurs at a younger age with associated high mortality and disability adjusted life years.

Available hospital based studies in Nigeria suggest there are rising rates of stroke in the country[154].

Available data, at least from hospital based studies, show that stroke accounts for 0.23%-4.0% of all hospital admissions, 0.5%-45% neurological admissions and 5%-17% of deaths on medical wards. It is the commonest cause of neurological admission in Lagos, the largest city and the commercial nerve centre of Nigeria. Cerebral infarction, intracerebral hemorrhage and subarachnoid haemorrhage, respectively, are responsible for 64%, 19% and 6% of strokes in the country[154].

In a community based study in Lagos[155], stroke prevalence was estimated as 1.14 per 1000 (1.51/1000 in men, 0.69/1000 in women and 24.1/1000 in those older than 65 years.

The mortality associated with stroke in Nigeria is high with 30 d case fatality ranging from 28% to 40%[154].

In a 10-year review of stroke in Sagamu, Ogun State, stroke accounted for 2.4% of all emergency admissions. Forty nine percent had cerebral infarction, 45% intracerebral haemorrhage and 6% SAH. The studies further showed that 1.8% of all deaths at the emergency room were due to stroke. Case fatality at 24 h, 7 d, 30 d and 6 mo were 9%, 28%, 40% and 46%, respectively[154]. In the year 2007, mortality from stroke in the country was put at 126/100 000 population[156].

In Nigeria, as in most developing countries, hypertension is the most important modifiable risk factor for stroke. It is present in almost 80% of cases. Unfortunately most victims are unaware of their blood pressure status prior to the event[157].

Hypertension as a risk factor for chronic kidney disease in Nigeria

Hypertension is a major cause of CKD and chronic renal failure (CRF) in Nigeria. In Enugu (South East) and Benin City (South South), hypertension is the commonest

cause of CKD and CRF[158,159]. It is only second to chronic glomerulonephritis in the South West[160-163]. Hypertension induced CRF in Nigeria is four times commoner in men than women with a male: female ratio of 4.3:1. Severe throbbing frontal headache and nocturia are common. The duration of hypertension is usually between 2-15 years. It is associated with a history of cigarette smoking, poor compliance to anti-hypertensive medications, family history of hypertension, severe/accelerated hypertension and severe uraemia. The presence of other hypertension related TOD, such as heart failure and retinopathy, is common. Mortality is high, 51% within the first 12 mo of diagnosis. Renal histological findings include glomerular sclerosis, malignant arteriolar changes and absence of glomerular cellular proliferation[164,165].

Hypertension and coronary artery disease in Nigeria

Hypertension is a major risk factor for coronary artery disease (CAD) in Nigeria. Anjorin *et al*[166] recently reviewed 87 patients with CAD seen over a period of 22 years (1983-2004) at the University of Maiduguri teaching hospital. Hypertension was identified as a risk factor in 53%, diabetes in 41%, cigarette smoking in 39%, hypercholesterolemia in 29% and obesity in 20%.

Hypertensive retinopathy in Nigeria

In a review of 407 patients with retinal diseases in Ile-Ife (Southwest) by Onakpoya *et al*[167], hypertensive retinopathy was responsible for 12% of cases. In Ibadan, hypertensive retinopathy is the 9th commonest cause of retinal diseases and responsible for 4.6% of cases[168]. It is also responsible for 7.7% of all retinal/optic nerve disorders and 0.1% of ocular disorders in a rural community in northern Nigeria. In Enugu (South East), hypertensive retinopathy is responsible for 13% of vitreoretinal diseases in a tertiary healthcare facility[169].

DISCUSSION

Since the creation of the Nigerian state in 1960, a lot of studies have been undertaken to provide information on the burden of hypertension in the country. This includes a national survey which was conducted in 1997[113]. It is pertinent, however, to note that most studies provided crude prevalence of the condition in the country. In addition, there are a lot of variations in the studies in terms of target population as well as criteria for diagnosis. Earlier studies used 160/95 mmHg (occasionally 160/90 mmHg) while the most recent ones used 140/90 mmHg as a cut off mark for the diagnosis of hypertension. The age structure in most of the studies is essentially middle age and represents the age structure of the Nigerian population, except in few studies that purely targeted middle age or elderly populations[15,23]. In many of the studies, the prevalence of hypertension was higher in men than in women at least up to the age of 40 years when the prevalence equalized[9,10,26,32]. This picture is similar to findings in other Africans, African Americans and in Blacks in the Caribbean[112].

The higher prevalence in the urban population may indicate differences in lifestyle. Urban populations are more likely to eat processed foods which are high in salt and fat content. Obesity which is a risk factor for hypertension is also higher in urban areas than in rural areas because of reduced physical activity.

In a few of the studies, especially in the Eastern part of the country, hypertension was found to be as high in the rural population as it is in the urban population[27]. This picture has been documented in some United States and European studies[170-173]. It is likely that those rural populations may be older as most old people move to rural areas after retirement from active service.

Hypertension awareness range from 3.5% in Sokoto to 30% in Nsukka[22,25,26,40,99]. There was no remarkable gender difference. Treatment ranged from 11.9%-21%[40,99]. In two studies the treatment rate was slightly higher in men than in women; however the control rate was significantly higher in women than in men (17.5% and 5%, respectively).

The higher detection rate in men than women is at variance with data from most parts of Africa and other parts of the world. Women are more likely to be detected during antenatal visits and are also more likely to accept the diagnosis of hypertension.

On the other hand, the blood pressure control rate is better in women than in men. Women are more likely to attend clinics for follow-up.

In general, hypertension and other chronic diseases awareness, treatment and control is generally low in the country as in most developing countries. These diseases are often asymptomatic and in most cases presentation is when complications have set in.

Emerging data from hospital studies show that hypertension or its complications is the commonest NCD in Nigeria. In 1961, hypertension related illnesses contributed to 8.8% of all medical admission in Lagos[28]. Abengowe *et al*[95] reported 9.3% in Kaduna in 1980. Recent data from the country indicated a rate of 28% in Port-Harcourt[124] and 21% in Benin City[119]. This is comparable to a rate of 30% from Tanzania[174].

In conclusion, hypertension in Nigeria today is the commonest risk factor for stroke, heart failure, ischemic heart disease and chronic kidney disease[175].

There is, therefore, a need to encourage health promotion in the population as means of primary prevention. There is also a need for increased public health education to increase the awareness of hypertension and the sequelae. Hypertension control programmes need to be established in communities in the country and more community based screening programmes for cardiovascular disease risk factors and NCDs need to be carried out. There is also a need to carry out research on the reasons for regional differences in prevalence of hypertension as well as reasons for lack of urban-rural differences in some areas in the country. The lack of scientific data to measure trends in the country should also be addressed.

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BRIEF ARTICLE

Global and segmental myocardial deformation by 2D speckle tracking compared to visual assessment

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Abstract

AIM: To examine the feasibility and reliability of measuring global and segmental longitudinal strain (LS) compared to visual assessment of wall motion (WM).

METHODS: Assessment of segmental (17 left ventricular segments) LS using automatic function imaging (AFI) in 55 patients (60.0 ± 8.7 years, 73% male) divided into 2 groups: group Ⅰ included 35 patients with WM abnormalities and/or impaired ejection fraction and group Ⅱ included 20 patients with normal WM and ejection fraction. Visual analysis of WM abnormalities was performed using 2-dimensional echocardiography (2DE) and WM score was calculated. Both modalities were analyzed by one expert reader at 2 different sessions.

RESULTS: Analysis of 935 left ventricular segments was completed in 94.1% and 96.3% by visual assessment and AFI, respectively. There was a strong positive linear relationship between the WM score and global LS in all patients. Intra-observer agreement for calculation of WM score was excellent for group Ⅰ patients (kappa: 0.97) and very good for group Ⅱ patients (kappa: 0.92). Intra-observer agreement for AFI showed excellent agreement with very small mean difference in both group Ⅰ and Ⅱ (-0.0 ± 2.3 and -0.0 ± 1.9, respectively).

CONCLUSION: The interpretation of global and segmental LS using AFI is a more feasible and reliable technique for the quantification of myocardial deformation than visual assessment of WM scores.

Key words: Speckle tracking; Wall motion abnormalities; Myocardial deformation

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INTRODUCTION

Echocardiographic evaluation of segmental and global myocardial function by visual assessment is the most used method[1]. The visual assessment relies mainly on myocardial radial performance, and is limited by high inter- and intra-observer variability. Furthermore, it provides a subjective evaluation of endocardial thickening and excursion[2]. Tissue Doppler imaging was expected to overcome these limitations, but its sensitivity to measure the longitudinal and radial deformation was limited due to the angle-dependancy with inability to differentiate between active and passive myocardial motion[3,4].

Speckle-tracking echocardiography (STE) is a new

noninvasive imaging technique that quantitatively analyzes global and regional myocardial function. Its evaluation is based on tracking natural acoustic reflections and interference patterns within an ultrasound window[5]. A large amount of published data has described the accuracy and clinical applications of STE with the ability to elaborate the myocardial deformation in longitudinal, radial and circumferential directions[6-8].

Automated function imaging (AFI) is a novel algorithm calculating the myocardial deformation from ultrasound speckles that is used to measure myocardial strain. It tracks the percentage of wall lengthening and shortening which helps to assess myocardial deformation based on grayscale images, similar in concept to magnetic resonance imaging tagging. It presents an objective, semi-automatic, and angle-independent analysis of longitudinal peak systolic strain (LS) based on speckle tracking and provides a single bull's-eye summary of the left ventricular (LV) segmental wall strain[9].

The objective of this study was to assess the feasibility and reliability of AFI compared with visual assessment by 2-dimensional echocardiography (2DE), regardless of underlying cardiac disorders.

MATERIALS AND METHODS

The study included 55 consecutive patients who were referred for echocardiography for assessment of LV function and segmental wall motion (WM) abnormalities. The inclusion criteria were adequate image quality and sinus rhythm. Conventional 2DE was performed according to guidelines using a commercial ultrasound system (Vivid 7, GE Health Medical, Milwaukee, WI, United States) supported by a multi-frequency transducer (M3S 1.7/3.4 MHz). After the completion of the 2DE study, the 17 LV segments were assessed by visual analysis and AFI. Both visual analysis and AFI were performed by one experienced observer at two different settings. The first analysis was performed immediately after the end of each study. The second re-analysis of all studies was performed by the same observer after collection of cases. The interval between the 2 analysis was 1 mo. In each study, the observer was blinded to the previous readings.

Visual analysis: Visual analysis of the contractile function of all the 17 segments was interpreted according to the American Society of Echocardiography criteria[10] using a four-point score: (1) normal; (2) hypokinetic; (3) akinetic; or (4) dyskinetic. The sum of the WM scores, averaged over the number of segments with interpretive scores, gave the WM score index.

AFI protocol: The AFI was performed through an offline analysis of 3 digitally stored 2D images (apical long-axis, 2- and 4-chamber) with high frame rates (> 60 frames/s) using commercial imaging analysis software (EchoPAC 6.1.0, GE Health Medical)[11]. The peak systolic strain values in a 17-segment LV model were used in the present study. End-systole was defined as aortic valve closure in the apical long-axis view by continuous Doppler wave recording. Automated delineation of endocardial borders was obtained through marking the mitral annulus level and at the apex on each digital loop. The area of interest was manually adjusted if automated delineation was not optimal. Segments with poor image acquisition or artifacts were excluded due to inability to measure LS. Segmental LS was calculated as the percentage of lengthening or shortening and the results for each plane were displayed (Figure 1). The results for all 3 planes were then combined in a single bull's-eye summary (Figure 2). The sum of LS, averaged over the number of segments with interpretive scores, gave the global LS. The normal values of segmental and global LS were considered (-17.4% for females and -15.9% for males) based on the Hunt study in Norway[12] which presented the reference values in 1266 healthy individuals according to age and sex.

Statistical analysis

Statistical analysis was performed using the software package SPSS version 11.5 (SPSS Inc, Chicago IL, United States). All data obtained were presented as mean ± SD. Paired sample *t* test was performed to determine the difference in values between the repeated readings of visual analysis and AFI. The level of significance was set to $P < 0.05$. Intraobserver agreement for visual analysis score for each segment was estimated using kappa values and classified as excellent with a value of 0.93-1.0, very good 0.81-0.92, good 0.41-0.60, and poor ≤ 0.4[13]. Intraobserver agreement for global and segmental LS measurements was estimated according to the Bland and Altman method[14].

RESULTS

Baseline criteria

The study included 55 consecutive patients (60.0 ± 8.7 years, 73% male). Depending on 2DE calculation of LV ejection fraction and assessment of WM abnormalities, the patients were classified into 2 groups: group I included 35 patients with WM abnormalities and/or impaired LV ejection fraction (≤ 50%), and group II included 20 patients with normal WM and LV ejection fraction. Baseline criteria of both groups are displayed in Table 1. Clinical data of patients in group I showed a higher incidence of diabetes, hypertension, smoking and ischemic heart disease (55%, 40%, 45% and 55%, respectively) than for patients in group II (30%, 25%, 30% and 15%, respectively). Through analysis of LV by the 17-segment model, a total of 935 segments were assessed by both visual and AFI analysis techniques. Global LS was well correlated ($R = 0.86$, $P < 0.0001$) with WM score index in all patients, while the correlation with LV ejection fraction was less ($R = 0.62$, $P < 0.01$).

Visual analysis

Complete analysis was achieved in all patients within 3.5

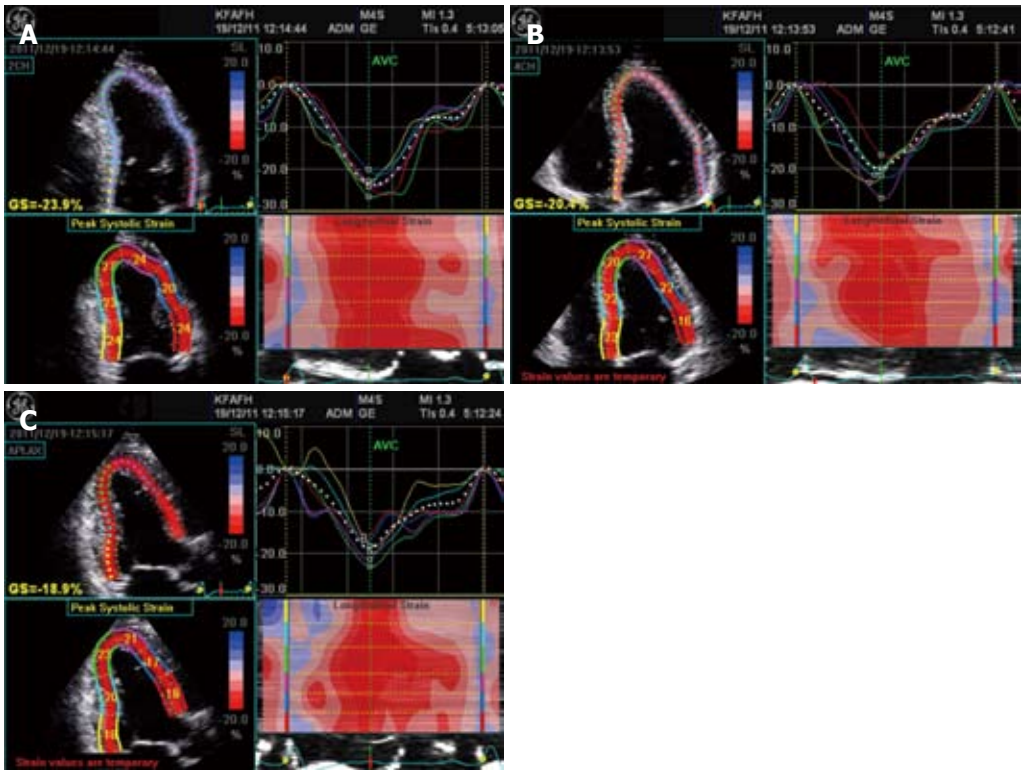

Figure 1 Segmental longitudinal strain displayed in 3 image planes. A: Apical 4-chamber; B: Apical 2-chamber; C: Apical long axis views.

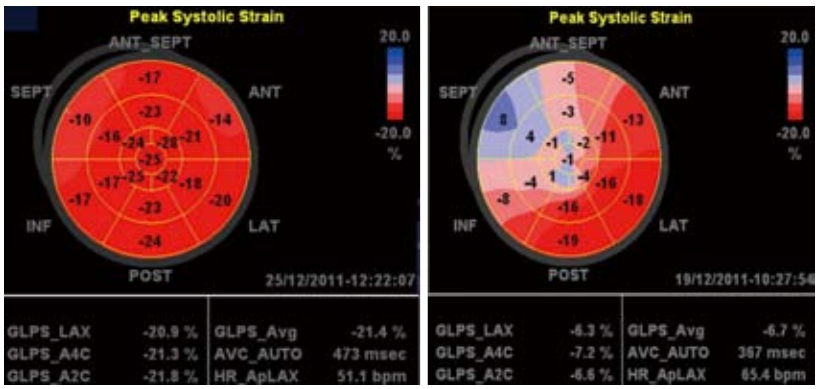

Figure 2 Measurements of longitudinal strain in all 17 left ventricle segments represented in bull's eye map in normal (right) and abnormal (left) subjects.

± 1.9 min. Complete scoring was obtained for 880 segments (94.1%), while it was not possible for 55 segments (5.9%) due to poor endocardial visualization. Distribution of the missed segments showed high incidence for basal antero-lateral (40%), basal anterior (20%) and apico-inferior (20%). The highest intra-observer correlation ($R > 0.8$, $P < 0.0001$) was obtained for analysis of mid segments of all walls, while the lowest correlation ($R = 0.56$, $P = 0.01$) was for both basal antero-lateral and basal anterior segments. Intra-observer agreement for calculation of WM score was excellent for group I patients (kappa value: 0.97) and very good for group II patients (kappa value: 0.92).

AFI analysis

Complete analysis was achieved in all patients within 3.9 ± 2.1 min. Manual modification of the endocardial border was performed to get optimal delineation in 10 patients (18%). Calculation of LS was obtained for 900 segments (96.3%), while it was not obtained for 35 segments (3.7%). Distribution of the missed segments showed high incidence for basal antero-lateral (26%), apico-lateral (20%), apico-inferior (20%) and basal anterior (14%). The highest intra-observer correlation (≥ 0.83, $P < 0.0001$) was obtained for analysis of apico-lateral, apico-septal, apico-inferior, mid antero-lateral, mid infero-septal and mid antero-septal segments. The lowest correlation ($R = 0.53$, $P = 0.008$) was for the basal antero-lateral segment. Basal and apical anterior segments showed low correlation ($R = 0.65$, $P = 0.001$). Using the Bland and Altman method for intra-observer agreement showed excellent agreement with a very small mean difference in both groups of patients (Table 2). Comparison between both techniques is summarized in Table 3.

Reclassification of patients

Based on global LS calculation, all patients in group I and 5 patients in group II had reduced global LS (-12.4% ± 2.1%).

Table 1 Baseline criteria of all patients

	Total (n = 55)	Group Ⅰ (n = 35)	Group Ⅱ (n = 20)	P value
Age	59.4 ± 13.6	61.0 ± 9.9	57.7 ± 16.9	0.4
Gender, n (%)				0.8
Male	29 (72.5%)	14 (70%)	15 (75%)	
Female	11 (27.5%)	6 (30%)	5 (25%)	
IVS (mm)	10.3 ± 2.4	9.4 ± 2.1	11.3 ± 2.4	0.01
PW (mm)	9.8 ± 1.7	9.4 ± 1.5	10.2 ± 1.9	0.1
LV mass	245.4 ± 99.5	254.9 ± 108.9	235.3 ± 90.6	0.5
LA diameter (mm)	38.3 ± 6.6	40.2 ± 6.4	36.3 ± 6.3	0.07
LVDD (mm)	51.2 ± 9.8	55.2 ± 11.6	49.0 ± 5.1	0.009
LVSD (mm)	36.4 ± 11.9	41.3 ± 14.1	30.2 ± 5.3	0.008
LV-FS (%)	30.0 ± 11.1	26.4 ± 11.9	34.9 ± 7.1	0.03
LVDV (mL)	119.4 ± 65.7	137.9 ± 85.8	99.9 ± 20.8	0.07
LVSV (mL)	65.7 ± 60.8	87.3 ± 77.3	40.9 ± 20.1	0.02
LV-EF (%)	49.9 ± 15.0	41.9 ± 14.1	59.7 ± 8.1	0.0001
WM score	20.6 ± 6.4	24.9 ± 6.4	16.0 ± 0.0	0.0001
WM score index	1.3 ± 0.4	1.6 ± 0.4	1.0 ± 0.0	0.0001
Global LS	-11.8 ± 6.7	-9.3 ± 7.1	-15.6 ± 3.7	0.02

Data ara show as mean ± SD. IVS: Interventricular septum; LA: Left atrium; LS: Longitudinal strain; LV: Left ventricle; LVDD: LV diastolic dimension; LVDV: LV diastolic volume; LV-EF: LV ejection fraction; LV-FS: LV fraction shortening; LVSD: LV systolic dimension; LVSV: LV systolic volume; PW: Posterior wall; WM: Wall motion.

Table 2 Intra-observer correlation and variability of segmental analysis by visual analysis and automatic function imaging

	Wall motion score			Speckle tracking (AFI)		
	Total (n = 55)	Group Ⅰ (n = 35)	Group Ⅱ (n = 20)	Total (n = 55)	Group Ⅰ (n = 35)	Group Ⅱ (n = 20)
1st reading	20.6 ± 6.4	24.9 ± 6.4	16.0 ± 0.0	-11.8 ± 6.7	-9.3 ± 7.1	-15.6 ± 3.7
2nd reading	22.6 ± 8.7	27.3 ± 5.9	17.7 ± 2.9	-13.6 ± 5.5	-11.3 ± 5.6	-15.6 ± 4.8
Correlation	R = 0.73, P = 0.03			R = 0.9, P < 0.0001		
MD	2.1 ± 5.9	2.4 ± 5.9	1.7 ± 2.9	-0.02 ± 2.0	-0.0 ± 2.3	-0.0 ± 1.9

Data ara show as mean ± SD. MD: Mean difference; AFI: Automatic function imaging.

Table 3 Summarized comparison between automatic function imaging and visual analysis of wall motion abnormalities

	Visual analysis	AFI
Analysis time (min)	3.5 ± 1.9	3.9 ± 2.1
Complete analysis (%)	94.10	96.30
Intra-observer mean difference		
Normal subjects	1.7 ± 2.9	-0.0 ± 1.9
Abnormal subjects	2.4 ± 5.9	-0.0 ± 2.3

Data ara show as mean ± SD. AFI: Automatic function imaging.

The remaining 15 patients in group Ⅱ had normal global LS (-17.8% ± 1.6%). The 5 patients in group Ⅱ with reduced global LS were older (62.1 ± 2.3 years), 4 males and 1 female. All were diabetic and hypertensive. 2DE showed borderline LV ejection fraction (51.2% ± 0.8%).

DISCUSSION

This study demonstrated that AFI analysis of global and segmental LS was well correlated with visual assessment of WM abnormalities. Compared to visual assessment, AFI showed very small intra-observer variability regardless of the presence or absence of WM abnormalities and impaired LV systolic function.

The visual interpretation of WM abnormalities with conventional 2DE is based on the assessment of myocardial thickening and endocardial excursion. This method is widely used for assessing LV global and segmental systolic function. However, it is observer-dependant and requires experience[1]. Several reports have described the reliability and feasibility of STE to evaluate global and segmental myocardial deformation throughout the cardiac cycle in both normal and abnormal subjects. It is able to investigate LV function (circumferential, radial and longitudinal) without angle dependency[15-17].

The AFI algorithm is a novel method based on 2D strain imaging which tracks acoustic pixels equally distributed within the myocardial wall. It enables the quantification of myocardial strain simultaneously in different LV segments with ultrasound beam angle-independency. Previous studies reported that AFI is a fast, simple and high reproducible tool for semi-automatic assessment of LV function that supports clinical decision-making[9,18]. The current study aimed to evaluate the reliability and feasibility of AFI to detect segmental WM asynergy compared with visual assessment.

In agreement with the studies of Reisner *et al*[18] and Munk *et al*[19], global LS was correlated better with WM score index than with LV ejection fraction (R = 0.86, P < 0.0001; R = 0.62, P < 0.01, respectively).This finding can be explained by the direct effect of LV volume and heart rate on calculation of ejection fraction, while this effect is minimal on WM score index and nil on global LS.

By AFI, complete analysis was obtained for 96.3% of segments while by visual analysis, it was less (94.1%). This was explained by the higher percentage of uninterpretable segments by visual analysis due to poor endocardial delineation, while AFI (which depends on objective tracking of pixels) originated predominantly from the sub-endocardial fibers[20]. Among the missed segments, basal antero-lateral and basal anterior had the higher incidence by both AFI and visual analysis, with tendency of better intra-observer correlation for AFI than visual analysis.

Theoretically speaking, the semi-automated calculation improves reproducibility of the technique when compared with objective assessment. This can explain the good intra-observer variability in measurement of global LS and LV rotation by 2D speckle tracking which was demonstrated in previous studies[18,21]. In the current study, excellent intra-observer correlation and agreement was shown by both techniques in normal subjects. In abnormal subjects, AFI showed better intra-observer correlation and agreement than visual assessment.

Reclassification of our patients based on global LS measurements showed that a considerable percentage (25%) of patients who were considered as normal due to absent segmental WM abnormalities had reduced global

LS. This was in agreement with previous studies[19,22] which demonstrated that quantification of segmental and global LS may detect subclinical LV dysfunction earlier than visual analysis of WM in asymptomatic patients with apparently normal LV ejection fraction.

The number of patients included is relatively small; however, it was enough to reach the target of the study. Only one software application (AFI) was applied for measurement of LS; therefore, our results must be taken in consideration towards the AFI only and not for other available software.

The AFI algorithm enabled a comprehensive assessment of global and segmental LS of the LV. It overcame the subjective and semi-quantitative analysis of LV obtained by visual assessment and showed better intra-observer agreement in both normal and abnormal subjects.

COMMENTS

Background

Speckle-tracking echocardiography is a new noninvasive imaging technique that quantitatively analyzes global and regional myocardial function. Its evaluation is based on tracking natural acoustic reflections and interference patterns within an ultrasound window. It presents an objective, semi-automatic, and angle-independent analysis based on speckle tracking and provides a single bull's-eye summary of the left ventricular segmental wall strain.

Research frontiers

Many algorithms are available for calculation of myocardial deformation. All algorithms tracks the percentage of wall lengthening and shortening which helps to assess myocardial deformation based on grayscale images, similar in concept to magnetic resonance imaging tagging. The study aimed to assess the feasibility and reliability of (AFI) algorithm for assessment of longitudinal strain using speckle tracking compared with visual assessment by 2-dimensional echocardiography. The study applied this algorithm in both normal and abnormal cardiac conditions.

Innovations and breakthroughs

The study demonstrated that AFI analysis of global and segmental longitudinal strain (LS) was well correlated with visual assessment of wall motion (WM) abnormalities. Compared to visual assessment, AFI showed very small intra-observer variability regardless of the presence or absence of WM abnormalities and impaired left ventricular (LV) systolic function. The study also showed that a considerable percentage (25%) of patients who were considered as normal due to absent segmental WM abnormalities had reduced global LS which mean that detection of myocardial abnormalities can be detected early.

Applications

This study directs towards improvement of the analysis and assessment of LV wall abnormalities using longitudinal strain as it is a more feasible and reliable technique than visual assessment of WM scores.

Peer review

This is an interesting article verifying the utility of Speckle tracking technique. The study is small but concludes that there is good correlation between visual estimates and AFI.

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Events Calendar 2012

January 18-21, 2012
Ninth Gulf Heart Association Conference
Muscat, Oman

January 27, 2012
ESC Global Scientific Activities at the 23rd Annual Conference of the Saudi Heart Association
Riyadh, Saudi Arabia

January 29–31, 2012
Integrated management of acute and chronic coronary artery disease
Innsbruck, Austria

January 30, 2012
Webinar on "Best of Euroecho 2011"
Sophia Antipolis, France

February 1-3, 2012
American Heart Association and American Stroke Association International Stroke Conference 2012
New Orleans, Louisiana, United States

February 3-5, 2012
6th Asian-Pacific Congress Of Heart Failure 2012
Chiang Mai, Thailand

February 9, 2012
4th British Society for Heart Failure Medical Training Meeting
London, United Kingdom

February 23–25, 2012
Advanced Invasive Cardiac Electrophysiology
Sophia Antipolis, France

February 24–26, 2012
International Congress of Cardiology
Hong Kong, China

February 28, 2012
Echocardiography evaluation of patient with multivalvular disease
Sophia Antipolis, France

February 29-March 3, 2012
Winter ISHNE 2012
Zakopane, Poland

March 8–10, 2012
Cardiac Pacing, ICD and Cardiac Resynchronisation
Vienna, Austria

March 8–10, 2012
24th Colombian Congress of Cardiology and Cardiovascular Surgery
Cali, Colombia

March 10-11, 2012
23rd International Meeting "Cardiology Today"
Limassol, Cyprus

March 14-18, 2012
Ninth Mediterranean Meeting on Hypertension and Atherosclerosis
Antalya, Turkey

March 15-17, 2012
e-Cardiology 2012
Osijek, Croatia

March 15-18, 2012
China Interventional Therapeutics 2012-CIT
Beijing, China

March 16-17, 2012
12th Annual Spring Meeting on Cardiovascular Nursing
Copenhagen, Denmark

March 16-17, 2012
3rd European Meeting: Adult Congenital Heart Disease
Munich, Germany

March 16-18, 2012
JCS2012 - The 76th Annual Scientific Meeting
Fukuoka, Japan

March 20–23, 2012
32nd International Symposium on Intensive Care and Emergency Medicine
Brussels, Belgium

March 25-29, 2012
16th International Symposium On Atherosclerosis 2012
Sydney, Australia

March 28–31, 2012
Rome Cardiology Forum 2012
Rome, Italy

March 28–31, 2012
Annual Spring Meeting of the Finnish Cardiac Society 2012
Helsinki, Finland

March 30-April 1, 2012
Frontiers In CardioVascular Biology 2012
London, United Kingdom

April 5-7, 2012
EAE Teaching Course on New echocardiographic techniques for myocardial function imaging
Sofia, Bulgaria

April 12-14, 2012
Cardiovascular Risk Reduction: Leading The Way In Prevention 2012
National Harbor, MD, USA

April 12-15, 2012
NHAM Annual Scientific Meeting 2012
Kuala Lumpur, Malaysia

April 18-21, 2012
World Congress of Cardiology Scientific Sessions 2012
Dubai, United Arab Emirates

April 19-21, 2012
Delivering Patient Care in Heart Failure
Sophia Antipolis, France

April 20-22, 2012
7th Clinical Update on Cardiac MRI and CT
Cannes, France

April 25-27, 2012
Angioplasty Summit 2012
Seoul, South Korea

April 25-28, 2012
The 61st International Congress of the European Society of Cardiovascular and Endovascular Surgery
Dubrovnik, Croatia

April 28-29, 2012
24th Annual Scientific Meeting of the SCS
Singapore, Singapore

May 3–5, 2012
EuroPRevent 2012
Dublin, Ireland

May 15–18, 2012
EuroPCR Congress 2012
Paris, France

May 17-20, 2012
2nd International Meeting On Cardiac Problems In Pregnancy 2012
Berlin, Germany

May 19-22, 2012
Heart Failure 2012
Belgrade, Serbia

May 23-26, 2012
46th Annual meeting of the Association for European Pediatric and Congenital Cardiology
Istanbul, Turkey

May 26-27, 2012
Cardiovascular Spring Meeting 2012
Vienna, Austria

June 7–9, 2012
6th Congress of Asian Society of Cardiovascular Imaging
Bangkok, Thailand

June 7-9, 2012
6th Congress of Asian Society of Cardiovascular Imaging 2012
Bangkok, Thailand

June 15–17, 2012
13th Annual Cardiology Update
Bhurban, Pakistan

June 21-24, 2012
10th International Pulmonary Hypertension Conference and Scientific Sessions 2012
Orlando, Florida, United States

July 19-22, 2012
13th Annual South African Heart Congress
Sun City, South Africa

August 16-19, 2012
60th annual scientific meeting of CSANZ
Brisbane, Australia

August 25-29, 2012
ESC Congress 2012
Munich, Germany

September 29-October 4, 2012
International Society of Hypertension 24th Annual Scientific Meeting 2012
Sydney, Australia

October 4-6, 2012
Magnetic Resonance in Cardiology
Riva Del Garda, Italy

October 20-23, 2012
Acute Cardiac Care 2012
Istanbul, Turkey

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GENERAL INFORMATION

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 362 experts in cardiology from 43 countries.

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The major task of *WJC* is to rapidly report the most recent developments in the research by the cardiologists. *WJC* accepts papers on the following aspects related to cardiology: arrhythmias, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, paediatrics, nursing, and health promotion. We also encourage papers that cover all other areas of cardiology as well as basic research.

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The columns in the issues of *WJC* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in cardiology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of cardiology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in cardiology.

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Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

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An informative, structured abstracts of no less than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no less than 140 words); RESULTS (no less than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312194155.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

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Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine con-

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REFERENCES

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The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h,

blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312200347.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/1949-8462/g_info_20100312192220.htm

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