Mean arterial blood pressure is one of the principal modifiable factors which contribute to arterial stiffness. The influence of antihypertensive drugs on arterial stiffness measured photoplethysmographically has not yet been studied. This pilot study was aimed at exploring the relationship between blood pressure (BP) and parameters of arterial stiffness on initiating antihypertensive treatment. Fourteen newly diagnosed hypertensive male or female patients aged 30 to 40 years participated in the study. The age, height, weight and body mass index was calculated for all patients. BP and arterial stiffness were measured once before treatment and weekly after initiation of treatment for 3 weeks. On comparing the pretreatment and post treatment weekly BP values, a highly significant decline in the systolic BP (p< 0.006) and mean BP (0.005) was observed, whereas diastolic BP showed a significant (0.016) decline. Post hoc analysis revealed that systolic BP (SBP) and diastolic BP (DBP) showed a significant decline (p = 0.011 and 0.027, respectively) at the second visit, which was around two weeks post treatment, while the mean BP showed a highly significant decrease (p = 0.009) at this time. However, pulse pressure and heart rate did not change significantly with treatment. Also, the parameters of arterial stiffness did not change significantly with treatment for the same duration. Thus, we concluded that reduction in BP in hypertensive patients as measured clinically by brachial cuff sphygmomanometry seems to be dependent on the encounter interval. The decrease in blood pressure occurred within three weeks, whereas changes in arterial stiffness do not occur even till three weeks of initiating the treatment.

Key words: Antihypertensive treatment, photoplethysmographic arterial stiffness, encounter interval.

INTRODUCTION

Increased arterial stiffness is a marker of cardiovascular damage, even in the absence of clinically apparent disease (Safar, 2000; Schiffrin, 2004). One of the principal modifiable factors that contribute to arterial stiffness is the mean arterial blood pressure (McEniery et al., 2005; Protogerou et al., 2007; Segers et al., 2009). The mean arterial blood pressure has a greater impact on the small to medium sized muscular arteries, leading to high peripheral vascular resistance (McEniery et al., 2007). As is expected, with an increase in arterial stiffness the compliance of the digital arteries is decreased in patients with essential hypertension (Bochmann et al., 1995).

Although pulse wave velocity as measured by applanation tonometry is considered the gold standard for measurement of arterial stiffness (Laurent et al., 2002), there are several other non invasive methods of measuring arterial stiffness.
the stiffness of the blood vessels. One easy to use and operator independent method is the photoplethysmographic assessment of pulse waveform, which is based on digital volume pulse (DVP) (Millasseau et al., 2000). It has also been suggested that stiffness index (SI) derived from the DVP can be used as a marker for risk stratification in untreated hypertensive patients (Chen et al., 2005). However, the influence of anti-hypertensive drugs on these arterial stiffness indices by photoplethysmographic method has not yet been studied. Therefore, we conducted a pilot study to explore the relationship between BP and parameters of arterial stiffness on initiating antihypertensive treatment.

MATERIALS AND METHODS

The study was performed at the Department of Physiology, Government Medical College and Hospital, Chandigarh. Newly diagnosed hypertensive patients from medicine outpatient department (OPD) were recruited for the study. Written informed consents were taken from the patients after explaining the nature of the study. Male or female patients between 30 to 40 years were included. Patients with chronic or acute alcohol and/or caffeine intake, smoking, history of cardiovascular disease, diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD), renal disease or patients on lipid lowering, blood sugar lowering or cardiovascular medications were excluded from the study. Pregnant or lactating females and females using oral contraceptive were also excluded from the study.

The heights of the patients were measured against a wall mounted inelastic measuring tape, with the patient standing erect with feet together. Weight was measured on a weighing scale with the patient in light clothing. The body mass index was calculated using the formula: Weight (kg)/ (Height)² (meters). Blood pressure and arterial stiffness were measured in supine posture in the right arm after the patient had rested for 15 min.

Measurement of blood pressure

Blood pressure (BP) was measured over the brachial artery of the right arm by auscultatory method using a conventional mercury sphygmomanometer. Measurements were taken after 15 min of rest in supine posture. Mean arterial pressure (MAP) was calculated using: DBP ± 1/3 pulse pressure. Pulse pressure was calculated as:

systolic pressure – diastolic pressure.

Measurements of arterial stiffness by digital volume pulse analysis

The digital volume pulse (DVP) analysis method is a noninvasive technique of measuring pulse wave reflections, in order to determine the peripheral arterial stiffness (Millasseau et al., 2006). Arterial stiffness, as measured by the DVP analysis method is a validated reproducible technique, with minimal intra observer variations (Chowienczyk et al., 1999; Sollinger et al., 2006). The stiffness index derived from this method has been demonstrated to have a good correlation with pulse wave velocity (PWV) (Sollinger et al., 2006). The sensitivity and specificity of this technique is comparable to the PWV method in the identification of patients with latent cardiovascular disease (Millasseau et al., 2002; Woodman et al., 2005).

Calculation of the stiffness index (SI) using pulse waveform reflections

The DVP waveform consists of a systolic peak and a second diastolic peak, which is formed by the reflection of the pulse wave from the small arteries in the lower body. The time delay – that is the peak-to-peak time (PPT) between the systolic and diastolic peaks is related to the transit time of pressure waves from the root of the subclavian artery to the apparent site of reflection and back to the subclavian artery. The degree of pulse wave reflection, which is the stiffness index (SI), depends on the impedance of the microvascular bed and the tone of the small-to-medium-sized blood vessels. This path length can be assumed proportional to height (h). Therefore, the SI can be calculated from the formula: SI = h/PPT (Oblouck, 1987).

Arterial stiffness measurement protocol

Arterial stiffness measurement of the healthy volunteers as well as patients was performed in the morning between 9 to 10 am following an overnight fast after refraining from caffeine-containing beverages, alcohol, and smoking in the previous 12 h. The DVP was recorded in the person’s right index finger. Volunteers rested for 15 min in supine posture in a temperature-controlled environment before the measurements were taken. All the volunteers were advised to refrain from talking and sleeping when the measurements were being taken. Recorded digital pulse waveforms were used (PCA 2; Micro Medical, UK) to generate indices of arterial stiffness using a standard validated protocol (Millasseau et al., 2006). Each person had at least three measurements (recorded for 30 s) taken 1 min apart, and an average was calculated and used for the analysis. Afterward, antihypertensive drug treatment was started: patients were given either an angiotensin II receptor antagonist or calcium channel blocker or thiazide diuretics. BP and arterial stiffness was measured weekly till three weeks in the manner mentioned earlier.

Statistical analysis

Blood pressure (BP) and arterial stiffness parameters in the hypertensive group were analyzed using analysis of variance (ANOVA) with post hoc analysis.

RESULTS

All results were expressed as mean ± standard deviation (SD). The total number of hypertensive patients was 14. The anthropometric parameters of newly diagnosed hypertensive patients are given in Table 1. Statistical analysis of the data obtained from the hypertensive group before and after treatment was done. On comparing the BP values before treatment and after each week of initiation of treatment for 3 weeks, a highly significant decline in the systolic BP (p< 0.006) and mean BP (0.005) was observed, whereas diastolic BP showed a significant (0.016) decline (Table 2). Multiple comparisons on post
Table 1. Anthropometric characteristics of hypertensive patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypertensive patients (n = 14; mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>64.3</td>
</tr>
<tr>
<td>Female (%)</td>
<td>35.7</td>
</tr>
<tr>
<td>Age</td>
<td>42.43 ± 7.89</td>
</tr>
<tr>
<td>Height</td>
<td>164.71 ± 7.77</td>
</tr>
<tr>
<td>Weight</td>
<td>74.93 ± 5.40</td>
</tr>
<tr>
<td>BMI</td>
<td>27.67 ± 5.74</td>
</tr>
</tbody>
</table>

Table 2. Pre and post BP treatment and indices of arterial stiffness in the hypertensive patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre treatment (n = 14)</th>
<th>1st week</th>
<th>2nd week</th>
<th>3rd week</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>159.0 ± 19.10</td>
<td>145.56 ± 7.99</td>
<td>136.75 ± 12.42</td>
<td>135.33 ± 9.24</td>
<td>0.006**</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>104.0 ± 14.86</td>
<td>97.56 ± 6.06</td>
<td>89.00 ± 8.21</td>
<td>87.33 ± 3.06</td>
<td>0.016*</td>
</tr>
<tr>
<td>PP</td>
<td>55.0 ± 4.31</td>
<td>48.00 ± 6.56</td>
<td>47.75 ± 7.96</td>
<td>48.00 ± 7.21</td>
<td>0.338</td>
</tr>
<tr>
<td>Mean BP</td>
<td>122.33 ± 14.95</td>
<td>113.56 ± 6.02</td>
<td>104.92 ± 9.07</td>
<td>103.33 ± 4.81</td>
<td>0.005**</td>
</tr>
<tr>
<td>HR</td>
<td>81.29 ± 13.80</td>
<td>77.11 ± 14.11</td>
<td>77.13 ± 13.87</td>
<td>75.33 ± 11.85</td>
<td>0.826</td>
</tr>
<tr>
<td>Stiffness index</td>
<td>9.56 ± 1.78</td>
<td>9.25 ± 2.08</td>
<td>8.32 ± 2.15</td>
<td>9.08 ± 1.76</td>
<td>0.641</td>
</tr>
<tr>
<td>Reflection index</td>
<td>68.30 ± 9.27</td>
<td>66.25 ± 15.85</td>
<td>65.29 ± 13.19</td>
<td>63.00 ± 15.59</td>
<td>0.924</td>
</tr>
<tr>
<td>Peak to peak time</td>
<td>176.70 ± 38.56</td>
<td>187.75 ± 38.87</td>
<td>208.71 ± 45.76</td>
<td>190.33 ± 7.39</td>
<td>0.459</td>
</tr>
</tbody>
</table>

* Significant; ** highly significant.

Hoc analysis revealed that the SBP and DBP showed a significant decline (p = 0.011 and 0.027, respectively) at the second visit, which is around two weeks post treatment and mean BP shows a highly significant decrease (p = 0.009) at this time. However, the pulse pressure and heart rate did not change significantly with treatment.

Representative pulse wave tracings as recorded in a hypertensive patient before the beginning of antihypertensive treatment (Figure 1) and at the end of three weeks of treatment (Figure 2) are shown. From these tracings also, not much difference in the pulse waveform (and thereby arterial stiffness) appears. Arterial stiffness was measurable in only 10 hypertensive patients. In the other 4 patients, on applying the probe, the message “stiff” was displayed on the screen. This occurs when the large arteries are very stiff so that the direct and reflected wave merges together, making it impossible to distinguish them. No diastolic inflection point can be found and the message “stiff” is displayed.

Furthermore, the pre treatment and post treatment peak to peak time (PPT) at two weeks shows an increase but it is not statistically significant. Other parameters such as SI and RI did not change significantly with treatment for the same duration. Pearson’s correlation and p value for different BP and arterial stiffness variables showed that there was a significant positive correlation between RI and SI (0.470) and a significant negative correlation between RI and PPT (-0.428). SI and PPT were highly significantly negatively correlated (-0.950). Pulse pressure was also significantly correlated with both SI (0.384) and PPT (-0.447), while HR significantly correlated with both SI (0.470) and PPT (-0.428).

DISCUSSION

The relationship between pulse wave velocity (PWV) and blood pressure showed that higher pressure will result in increased PWV as found by Young (1809). For this reason, it would be expected that drug interventions that decrease blood pressure would be associated with a fall in PWV. This has been demonstrated with a range of antihypertensive drugs. However, in these studies, the encounter interval between the doctor and the patient after initiating treatment was > 1 month. In this study, we followed the patients at weekly intervals after initiating antihypertensive treatment in order to determine the relationship between normalization of BP and arterial stiffness. In the hypertensive group, it was seen that by two weeks of treatment the SBP, DBP and mean BP of the patients showed a statistically significant decline and by the third week of treatment the blood pressure showed no further decline. However, the arterial stiffness parameters showed no change in the entire 3 weeks duration of treatment. The currently recommended encounter interval after initiating treatment in hypertensive patients is 1
month (Jones and Hall, 2004) and this is based largely on expert opinion. However, in a study by Turchin et al. (2010), the difference in time to blood pressure normalization persisted at encounter intervals shorter than the currently recommended. In this study, it was found that in patients with an average encounter interval $\leq 2$ weeks BP normalized after a median of 0.7 months. This was also seen in our study. For an encounter interval of 1 to 2 weeks, the rates of decrease for systolic and diastolic blood pressures were 43.8 and 13.1 mm Hg/month, respectively (Turchin et al., 2010). From recent research, it is evident that shorter encounter intervals causes faster BP reduction; therefore, if shorter encounter intervals are to be achieved, more creative approaches to patient care are needed (Okie, 2008).

We also observed that although BP normalized in our patient by the end of third week of initiating the treatment, yet there was no alteration in the parameters of arterial stiffness at this time. This indicates that despite mean BP being a major contributor to arterial stiffness, its reduction after initiation of antihypertensive therapy does not go hand in hand with parameters of arterial stiffness.
Probably arterial stiffness takes a longer time to decrease as compared to blood pressure. Physiologically, the stiffness of the large arteries depends on 3 main factors: structural elements within the arterial wall, such as elastin and collagen; distending pressure and vascular smooth muscle tone (McEniery et al., 2006). In single dose or short-term studies, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), selective beta1-blockers, beta-blockers with vasodilating properties and some diuretics could improve arterial stiffness (Blacher et al., 2005; Van Bortel et al., 1995). However, it is not clear whether this effect was limited to the decrease in blood pressure, or whether also an effect beyond the effect of blood pressure reduction was present.

After a 6-month treatment period for a similar reduction in blood pressure, the ACEI perindopril showed a more pronounced improvement of carotid artery stiffness than the diuretic amiloride/hydrochlorothiazide (Kool et al., 1995), showing that the de-stiffening potency differs between antihypertensive drugs and suggesting that some may have an effect beyond the effect due to blood pressure decrease. Moreover, a meta-analysis by Ong et al. (2011) revealed that in short-term studies (defined by the authors as a duration <4 weeks), only ACEIs reduced PWV beyond the blood pressure effect, whereas in long-term studies (4 weeks or more), all studied drug classes were effective. Vasodilation may at least in part account for the effect beyond blood pressure reduction of vasoactive drugs such as ACEI, ARB, CCB and beta-blockers with vasodilating properties. However, the mechanisms by which diuretics and selective beta1-blockers would reduce stiffness beyond blood pressure values are unknown. It was also observed that the effect for selective beta1-blockers and diuretics on PWV was comparable to the vasoactive drug classes (Ong et al., 2011). This may suggest that apart from the antihypertensive property of the antihypertensive drug, the sustained unloading of the arteries by blood pressure reduction itself may contribute to structural de-stiffening of arteries within a few months.

Since several mechanisms may be involved in producing reductions in arterial stiffness with a given treatment, assessment of arterial stiffness has to be distinguished between the effects of acute, short-term, or long-term chronic treatments. For example, after acute administration of an antihypertensive drug, improvement of arterial stiffness is principally related to functional or mechanical mechanisms such as reduction of distension pressure, reduction of smooth muscle tone, enhancement of endothelial functions, whereas after long-term chronic treatment, additional mechanisms can be involved; for example changes in the arterial geometry and structure, reduction in degree of fibrosis, increase in elastin/collagen ratio, remodeling of the arterial wall (Laurent et al., 2006). Experts agree that assessment of arterial stiffness after a long-term treatment period should be preferred because of the underlying patho-physiological mechanisms involved and because acute effects may not predict long term efficacy (Bortela et al., 2011).

Conclusion

From this pilot study, it was concluded that reduction in BP in hypertensive patients as measured clinically by brachial cuff sphygmomanometry seemed to be dependent on the encounter interval. The decrease in blood pressure in hypertensive patients occurred earlier within three weeks as compared to the changes in arterial stiffness, which did not occur even till three weeks of initiating the treatment.

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