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Original Article

The power combination of blood-pressure parameters to predict the incidence of plaque formation in carotid arteries in elderly

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Abstract: Hypertension is considered as one of the major risk factors of atherosclerosis, especially for carotid artery plaque, which is a sign for cardiovascular incapacity and cerebral infarction. As adult age, systolic blood pressure (SBP or S) tends to rise and diastolic blood pressure (DBP or D) tends to fall, thus the pulse pressure (PP) will increase. The vascular injury was directly proportional to the level of SBP, and inversely proportional to DBP. But so far, studies of the vascular injury based on SBP and DBP measurement were mostly qualitative. The exact contribution of each parameter to the vascular injury has not been quantitatively identified. In this study, we employed a mathematical model to predict the risk for plaques of carotid arteries in aged people and combined the SBP, DBP and heart rate (HR) to perform a quantitative analysis. We analyzed 1672 males who were over 60-year-old and hospitalized due to atherosclerosis-related diseases and received a 24-h arterial blood pressure monitoring (ABPM) examination. These patients were divided into 19 subgroups using the ABPM data, 24-h average SBP, DBP and HR as variables based on the ascending order of the magnitude of each element. We developed a new index, namely the dynamic level (DL) which correlated best with the plaque formation of carotid arteries among all the well-established indexes for blood pressure. We demonstrated that index DL has better correlation to plaques incidence tendency ($p < 0.0001$) when compared to either SBP ($P < 0.05$) or PP ($P < 0.001$) alone. The risk on incidence of the plaques of carotid arteries has positive correlation with first power of SBP and -0.8 power of DBP. This model can be used clinically to predict the occurrence of plaque formation.

Keywords: Blood pressure parameters, the plaques of carotid arteries, mathematical method, vascular injury

Introduction

Hypertension, which is widely distributed in general population, is known as a major risk factor for carotid artery plaque formation. Previous research indicated that efforts to control blood pressure (BP) and limited vascular injury rely heavily on diastolic blood pressure (DBP or D) reduction [1]. However very recent data debated that systolic blood pressure (SBP or S) as well as pulse pressure (PP) and heart rate (HR) played even more important role in the progression of vascular injury [2-5]. The Framingham study made a longitudinal follow-up of patients over 50 years of age and found that increased PP was in close association with cardiovascular and cerebrovascular events [6, 7]. However, two other recent studies have shown that PP was less useful in predicting stroke risk than SBP [8, 9]. These controversies raise an important question: is single parameter suitable for predicting vascular injury? Although the relationship between vascular injury and SBP, DBP, HR and PP has been established individually and qualitatively, the relative contribution of each parameter on the incidence of vascular injury has not been analyzed systematically and quantitatively. Consequently, it is still remain unclear to what extent the SBP, DBP, PP and HR should be reduced in order to

minimize the incidence of vascular injury. The main purpose of the present study is to find out the quantitative correlation between vascular injury and blood pressure's parameters by mathematical analysis using a large patient population.

Materials and methods

Participants

We retrospectively analyzed 1672 elderly-male-patients cases and compared the impact of main BP parameters such as SBP, DBP, PP and HR with the risk of vascular injury. The patients who visited the Geriatrics of Xin Hua Hospital Affiliated to Shanghai JiaoTong University School of Medicine, China for the reason of atherosclerosis-related diseases were selectively included in the study. The selected objects excluded patients with various acute diseases and advanced stage of malignancy or valvular heart diseases.

Study design

In this study, besides taking the normal biochemistry examination after hospitalization, the patients also underwent a 24-h arterial blood pressure monitoring (ABPM). The facility recorded the SBP, DBP and HR every 30 mins in daytime and 60 mins nighttime. The PP is defined by the difference between SBP and DBP. We also determined the max, min and average values of SBP, DBP and HR in 24 hours. We used the average SBP, DBP and HR values measured in past 24-hour as variables and defined their power product $\frac{S \times HR^x}{D^y}$ as a new index DL (dynamic level of blood pressure). Then we obtained not only the directly measured BP index such as average SBP or S value, average DBP or D value, average HR value, but also calculated BP index PP value as PP = S-D. Furthermore, we deduced dynamic level value *DL*, as defined by $DL = \frac{S \times HR^x}{D^y}$ following the protocol described previously [10, 11].

We gained 1672 different DL values according to that new dynamic level value definition. After obtaining 1672 DL values corresponding values from 1672 patients, we divided these new dynamic level index DL into 19 sub-groups by incremental manner. Each DL average value with incidence of the plaques of carotid arteries would be a data point. Thus we will get 19 data points. In consideration of many disturbing factors which occurred in the clinic data setting, the 19 data points which reflected the trend of incidence of the plaque formation in carotid arteries from 1672 patients would distribute around a supposed 'smooth curve' randomly. This 'smooth curve' is a curve used to reflect the variation trend for this set of data as described in ref. [10, 11]. The difference between 'smooth curve' and discrete data would be used to judge whether it is a good trend to represent the dependence of CI's incidence on the new index *DL*. The smaller the difference between 'smooth curve' and discrete data were the better clinical value they represented. If we used the mathematical expression for this difference, i.e. the difference between the incidence of plaque formation in carotid arteries F_i and the corresponding value in 'smooth curve' f_i, the standard error definition will be used as follows [10, 11].

$$\sigma = \sqrt{\frac{\sum_{i=1}^{n}(F_i - f_i)^2}{n}} \quad (1)$$

where n is 19 in this paper.

In this paper, the less of the value of *s* has the better clinic validity for that set of 19 data points resulted from the *DL* value with the fixed values of *x* and *y*. Then we should find a set of *x* and *y* value which gave the minimum of *s* to give the best clinical validity of new index DL.

Statistical analysis

All variables were analyzed using the SPSS 16 statistical package (SPSS Inc., Chicago, IL, USA). Statistical significance was evaluated using unpaired Student's t test for comparisons between two means. The comparison patients' clinical characteristics of plaque group and non-plaque group, which has an asymptotic chi-square distribution. Mean ± SD is expressed; $P<0.05$ is considered statistically significant.

Results

Risk factors contribute to the development of plaque formation in carotid arteries

1672 elder-male-patients were divided into plaque group and non-plaque group. We found that the average ages of the patients from plaque group was higher than that of the non-

Table 1. Clinic characteristics of the studied population

	no plaques	plaques
Number	995 (40.1%)	666 (59.9%)
Age (years)	79.1 ± 6.4	81.1 ± 4.9***
Hypertension	722 (72.6%)	575 (86.3%)***
High Blood Lipids	295 (29.6%)	235 (35.3%)*
Diabetes Mellitus	238 (23.9%)	212 (31.8%)***
Cardiovascular Disease	801 (80.5%)	542 (81.4%)
Cardiac Arrhythmia	646 (64.3%)	347 (66.5%)
Lacunar Infarction	79 (7.9%)	497 (74.6%)***
left ventricle hypertrophy	263 (26.4%)	223 (33.5%)**
Carotid Plaques	615 (61.8%)	484 (72.7%)***
Lower Limbs' Plaques	640 (64.3%)	520 (78.1%)***

*p < 0.05; **P < 0.01, ***P < 0.001; plaques: plaques of Carotid Arteries.

plaque group (81.1 ± 4.9 versus 79.1 ± 6.4 years, P < 0.001). It was also showed that patients who were affected with hypertension, hyperlipidemia, diabetes mellitus, cardiovascular disease, left ventricle hypertrophy, lacunar infarct, cerebral infarction and lower limbs' plaques have a higher incidence of plaque formation in plaques of carotid arteries (**Table 1**).

The influence on plaque formation by BP and HR

As shown by **Table 2**: the incidence of plaque formation in carotid arteries is directly proportional to the SBP, PP and inversely proportional to DBP, with no obviously correlation with HR. We found that the 24-hour SBP average value (128.6 ± 14.5 vs 133.6 ± 15.6 mmHg; P < 0.001), maximum SBP value (160.4 ± 21.0 vs 164.6 ± 22.3 mmHg; P < 0.01), and minimum of SBP (100.5 ± 15.4 vs 102.9 ± 15.4 mmHg; P < 0.01) were all higher in the plaque group compared to the non-plaque group (**Table 2**). Similarly, the 24-hour average PP value (57.5 ± 12.0 vs 59.9 ± 11.3 mmHg, P < 0.001), maximum of PP (79.6 ± 13.2 vs 83.5 ± 16.3 mmHg; P < 0.001) and minimum of PP (36.1 ± 10.4 vs 37.8 ± 14.6 mmHg P < 0.01) were all higher in the plaque group. There was no statistical difference between the plaque group and non-plaque group in terms of the average of DBP, DBP maximum and minimum value, and HR value (**Tables 2** and **3**). In the mathematical analysis using the formula (1), we obtained 1672 patients' *DL* values after trying each set of *x* and *y*. Based on these *DL* values, 19 sub-groups' incidence of plaque formation F_i from these patients were subsequently obtained. In each sub-group *i* one has the average value of DL (AVE_i). The Y-axis was defined as F_i and X-axis as AVE_i. These nineteen data sets formed 19 discrete points in this X-Y coordinate system. The tendency formed by these points could be expressed by smooth curve using the typical mathematical method given in ref. [9]. Throughout thousands of tempts to the sets of *x* and *y*, it was interesting that the minimum value of s would happen when $x = 0.2$ with $y = 0.8$. Thus we believe that new index DL defined as $DL = \frac{S \times HR^{0.2}}{D^{0.8}}$ was the best expression, which associated to the incidence of plaque formation. The calculation shows the good association of this index *DL* with incidence of plaque formation in carotid arteries with p < 0.0001.

Figure 1 showed the relationship between new index *DL* value and incidence of plaque formation in carotid arteries. We used the ratio of *DL* and DL_{max} (DL/DL_{max}) as the X-axis and incidence of plaque formation in carotid arteries as Y-axis. We calculated *DL* values according to the optimized definition of $DL = \frac{S \times HR^{0.2}}{D^{0.8}}$ from the 24-hour average BP indexes in 1672 patients. And then, those *DL* values were arranged in incremental manner and came up with 19 sub-groups. With smooth curve method taken, the basic tendency curve would form by those discrete data (shown in red solid line). The 19 incidences of disease data deduced from 1672 patients were shown with black dot. These discrete points showed good match with change tendency we obtained above. When the X-axis changed from 0.4 to 1, the incidence of plaque formation in carotid arteries would increase from 23% to 42%, with chance of plaque formation in carotid arteries increased by 19%. The anastomose degree could be expressed by formula (1). And the calculated standard deviation is σ = 0.015. The correlative degree between the 'smooth curve' and discrete points is R = 0.85, with P < 0.0001.

From **Figure 1A**, the incidence of plaque formation in carotid arteries increased by 19% as X-axis changed from 0.4 to 1, and the average deviation value was about 2% between measured value and smooth curve. The increase of 19% in incidence of plaque formation in carotid

Table 2. Demographic and clinical characteristics of subjects at Index blood pressure according to subsequent plaques of carotid Arteries

	No plaques	plaques
Systolic BP, SBP (mmHg)		
SBPave	128.6 ± 14.5	133.6 ± 15.6***
SBPmax	160.4 ± 21	164.6 ± 22.3**
SBPmin	100.5 ± 15.4	102.9 ± 15.3**
Diastolic BP, DBP (mmHg)		
DBPave	71.3 ± 8.2	71.7 ± 8.3
DBPmax	92.8 ± 11.9	93.0 ± 13.0
DBPmin	51.6 ± 8.1	52.2 ± 6.4
Pulse Pressure, PP (mmHg)		
PPave	57.5 ± 12.0	59.9 ± 11.3***
PPmax	79.6 ± 13.2	83.5 ± 16.3***
PPmin	36.1 ± 10.4	37.8 ± 14.6**

*p < 0.05; **P < 0.01, ***P < 0.001; plaques: plaques of carotid arteries. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; ave: the average numerical value of 24-hour; max: the maximum numerical value during 24-hour; min: the minimus numerical value during 24-hour.

Table 3. Index heart rate of patients according to subsequent plaques of carotid arteries

	no plaques	plaques
Heart Rate, HR (bpm/min)		
HRave	73.1 ± 11.0	72.9 ± 10.6
HRmax	93.2 ± 17.3	92.6 ± 17.4
HRmin	58.3 ± 11.2	59.1 ± 10.4

HR: heart rate; plaques: plaques of Carotid Arteries. ave: the average numerical value of 24-hour; max: the maximum numerical value during 24-hour; min: the minimus numerical value during 24-hour.

arteries is much greater than the deviation value. So it could be applied to guide clinical practice. When the X-axis value is smaller than 0.7, the incidence of plaque formation in carotid arteries would increase linearly. When the X-axis value was bigger than 0.7, the incidence of plaque formation would increase sub-linearly.

As comparison, we checked the correlation of the typical BP index with incidence of plaque formation in carotid arteries. The data of the typical BP index such as SBP, DBP, PP, HR was divided into 19 sub-groups in incremental manner with method taken above. The average value of the indexes and their incidence of disease from each sub-group were obtained. Thus, these 19 sub-groups showed the trend of incidence of disease with change of SBP, DBP, PP, and HR. These data were in line with the change of incidence of plaque formation in carotid arteries analyze in statistic shown by **Figure 1B-E**. Our results indicated that PP value and SBP value had positive correlation with incidence of plaque formation in carotid arteries.

Figure 1B shows the relationship chart between average of SBP and incidence of plaque formation in carotid arteries. We defined the ratio of average SBP and its maximum value in 19 data (S/S_{max}) as X-axis, as well as the incidence of plaque formation in carotid arteries as Y-axis. The 24-hour average SBP value with incremental manner from 1672 patients formed 19 sub-groups. The data was analyzed as the same way as the DL values so it can be deduced 'smooth curve' from those discrete dots of incidence of plaque formation in carotid arteries (Shown in red solid line). The 19 incidences of plaque formation were shown on the figure with black dots. These discrete dots have certain association with the 'smooth curve', which was supposed to reflect the trend by these discrete dots. When the X-axis changed from 0.6 to 1, the incidence of plaque formation increased from 32.5% to 45%, with chance of plaque formation increased by 12.5%. The anastomose degree expressed by the standard deviation is σ = 0.042, which is 2.8 times larger than that of new index DL. The correlative degree between 'smooth curve' and discrete points is R = 0.66, with P = 0.02. The correlative degree reflected the fact that the association between average value of SBP and incidence of plaque formation is not as good as the new index $DL = \frac{S \times HR^{0.2}}{D^{0.8}}$.

Figure 1C shows the relationship chart between normal average PP and incidence of plaque formation. Similar to the analysis for SBP, the ratio of average pulse pressure and its maximum value in 19 data (P/P_{max}) as X-axis, the incidence of plaque formation in carotid arteries as Y-axis. When the x-axis changed from 0.42 to 1, the incidence of plaque formation increased from 32.5% to 46.5%, with chance of plaque formation in carotid arteries increased by 14%. The calculated standard deviation is σ=0.049.

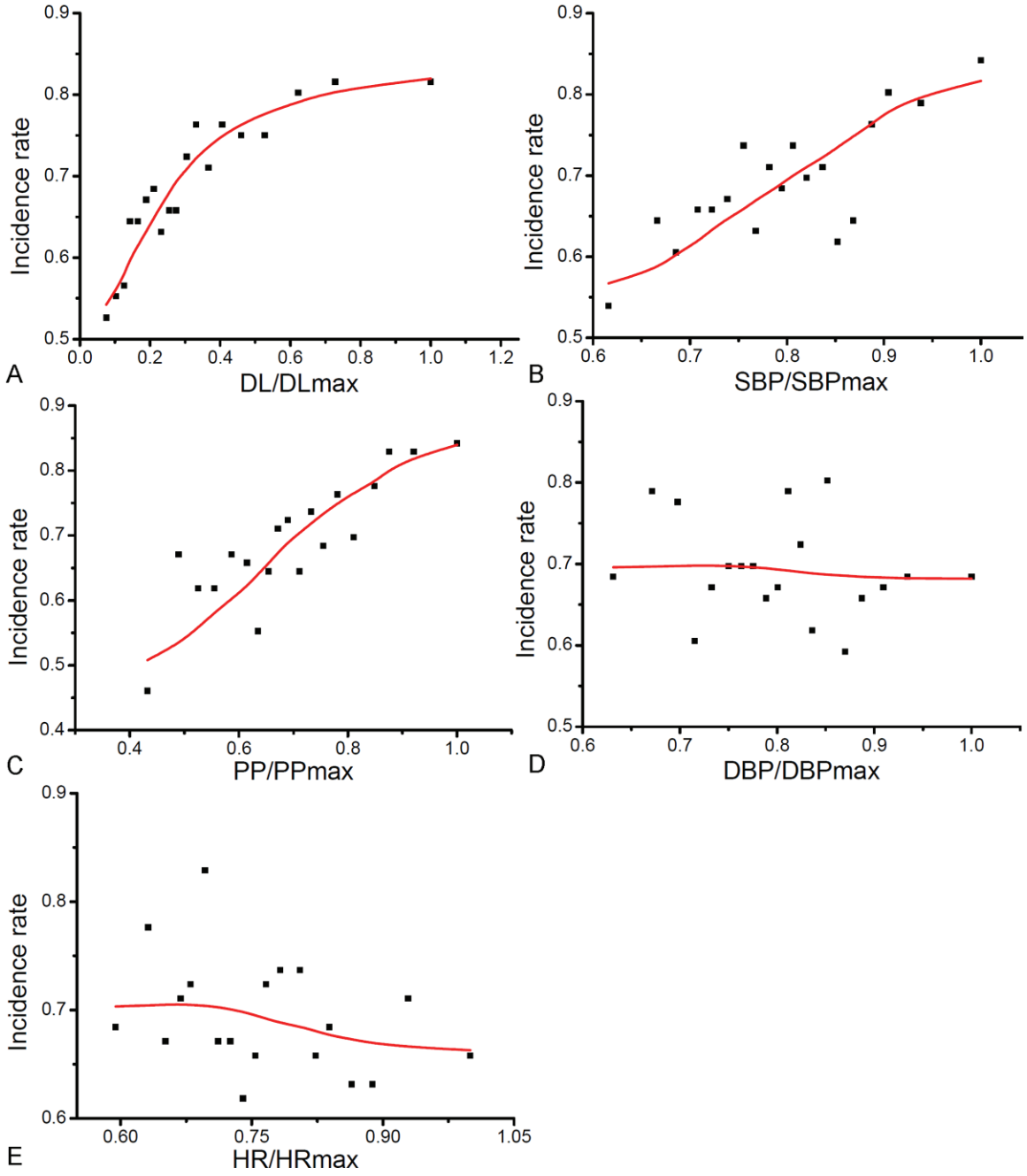

Figure 1. A: The relationship between the new index of blood pressure: dynamic level (DL) $\frac{S \times HR^{0.2}}{D^{0.8}}$ and incidence of plaques of Carotid Arteries. DL: the new blood pressure index proposed in this paper as dynamic level index: $DL = \frac{S \times HR^{0.2}}{D^{0.8}}$; DLmax: the maximum of the DL value. The basic trend curve would form by those discrete data (shown in red solid line) and the 19 incidences of disease data deduced from 1672 patients have been shown with black dot. The standard error defined by Equation 1 is σ = 0.015. The correlative degree between the trend curve and discrete points is R = 0.85, with P < 0.0001. B: The relationship between systolic blood pressure and incidence of plaques of Carotid Arteries. SBP: systolic blood pressure; SBPmax: the maximum of SBP. The basic trend curve would form by those discrete data (shown in red solid line) and the 19 incidences of disease data deduced from 1672 patients have been shown with black dot. The standard error defined by Equation 1 is σ = 0.042. The correlative degree between the trend curve and discrete points is R = 0.66, with P = 0.02. C: The relationship between pulse pressure and incidence of plaques of Carotid Arteries. PP: pulse pressure; PPmax: the maximum of PP. The basic trend curve would form by those discrete data (shown in red solid line) and the 19 incidences of disease data deduced from 1672 patients have been shown with black dot. The standard error defined by Equation

1 is σ = 0.049. The correlative degree between the trend curve and discrete points is R = 0.68, with P = 0.001. D: The relationship between diastolic blood pressure and incidence of stroke DBP: diastole blood-pressure; DBPmax: the maximum of DBP. The basic trend curve would form by those discrete data (shown in red solid line) and the 19 incidences of disease data deduced from 1526 patients have been shown with black dot. The standard error defined by Equation 1 is σ = 0.054, and without statistic validity between the average diastole blood-pressure and incidence of plaques of Carotid Arteries. E: The relationship between heart rate and incidence of stroke. HR: heart rate; HRmax: the maximum of HR. The basic trend curve would form by those discrete data (shown in red solid line) and the 19 incidences of disease data deduced from 1526 patients have been shown with black dot. The standard error defined by Equation 1 is σ = 0.056. The *P* value shows that there is no statistic correlation between the heart rate and the incidence of plaques of Carotid Arteries.

Table 4. The relationship between indexes Blood Pressure and trending curve of patients plaques of Carotid Arteries

	SBPave	DBPave	PPave	HRave	$S \times HR^{0.2}/D^{0.8}$
P	0.018	0.68	0.001	0.6	< 0.0001
r	0.67	-0.06	0.71	0.15	0.88
σ	0.045	0.051	0.05	0.06	0.013

P: test of hypothesis; r: correlation; s: standard error. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; ave: the average numerical value of 24-hour; max: the maximum numerical value during 24-hour; min: the minimus numerical value during 24-hour.

The correlative degree between the 'smooth curve' and discrete points was R = 0.68, with P = 0.001. Compared with the statistic value of the new index *DL*, we found that the new index *DL* had a much better correlation with the incidence of plaque formation in carotid arteries compared with the index of PP or SBP.

Figure 1D and **1E** showed the relationship charts between DBP or HR and incidence of plaque formation in carotid arteries. Similar to **Figure 1A**, we defined (D/D_{max}) or (HR/HR_{max}) as X-axis, the incidence of plaque formation in carotid arteries as Y-axis. The standard deviation for SBP and HR were σ = 0.054 and 0.056, respectively. There was no statistical validity between the SBP or HR and incidence of plaque formation in carotid arteries.

In comparison of normal BP indexes with our new index $DL = \frac{S \times HR^{0.2}}{D^{0.8}}$ comprehensively, we could make a conclusion that the new index has better association with incidence of plaque formation in carotid arteries. The statistic parameters for different index of BP are listed in **Table 4**. It was clear that only *DL* index, *P (ave), S (ave)* with P < 0.05, giving the statistic validity on change tendency. The P value for *DL, P (ave),* and S *(ave)* are < 0.0001, 0.001, 0.02, respectively. As we all know, the *P*-value is quantile of the value of the test statistic. The more stringent *P*-value is, the better clinic value it represents. Using *DL* index to predict the incidence of plaque formation in carotid arteries gave the most valuable clinical reference meaning with PP and SBP better, DBP and HR worse. The numeric type data such as age, BP and HR pass the test of normality exam (**Table 4**).

Discussion

It is known that hypertension, HL, DM and aging are the main risk factors for the development of atherosclerosis and plaque formation in carotid arteries [12-18]. Our data indicated that the elevation of SBP and PP but not DBP and HR is associated with increased incidence of plaque formation in carotid arteries. The new index *DL* described synthetical effect of the BP by including all three directly measured indexes (SBP, DBP and HR). To our knowledge, this was the first model system that integrated all three risk factor and could be used clinically to guide clinicians in hypertension management.

We had proven that our mathematical method was suitable to predict in cerebral infarction [10] . Meanwhile, another study has shown that a long-term elevation of BP by 9/5 mmHg would increase the incidence of plaque formation in carotid arteries by 30% [16]. On the other hand, when the BP decreases by 5-6 mmHg in average, the incidence of plaque formation in carotid arteries could decrease by 35-40% [14]. These findings were in line with our data that increased SBP was associated with increased incidence of THE plaque formation in carotid arteries [19]. During the process of aging, the major arteries become hardening and eventually lead to increased vascular resistance. SBP but not DBP increases continually during this process [20]. The increase of SBP lead to the increase of the new index *DL* which is associ-

ated with increased incidence of plaque formation in carotid arteries. This effect has been reflected by the fact that with the increase of age the incidence of plaque formation in carotid arteries will be increased as well.

In the young people, both SBP and DBP would increase parallely [21]. But in middle-aged people, the increase of SBP is much more than that of the DBP [7], and consequently, the PP is augmented. The PP is an independent risk factor of Cardio-cerebral-vascular system diseases and it has a better prediction value than SBP and DBP [22]. The increase of PP will results in an increased pressure on vessel wall [22]. Eventually, the elastic component of vessel wall become fragmented and leads to the formation of aneurism [23]. The increase of PP also increases the power of shear stress and tension draft power on the vessel wall [22]. This will result in vessel injury and lead to atherosclerosis and thromboangiitis [24]. Arteriosclerosis will increase pulse pressure even further and vice versa. Our research confirmed previously studies using qualitative approach that the risk of plaque formation in carotid arteries had a positive correlation to SBP and PP. Furthermore, our study had found that the incidence of plaque formation in carotid arteries had positive correlation with first power of SBP and -0.8 power of DBP.

In the situation with no change in stroke output and outside resistance, the acceleration of heart rate with diastole period shortened and decreased quantity of blood-stream from artery would cause the increase of blood quantity remaining in main artery in end of diastole [24]. This would lead to the increase of DBP. At the end of diastole, the increase of blood quantity in main artery would cause the future increase of blood quantity in systole with SBP increased. But the increased range of systole is smaller than diastole [25]. According to the data from Chicago and Framingham studies [26, 27], the increase of HR has a close relationship with cardiovascular events. But in our study we found that there was no correlation between heart rate and plaque formation in level of statistic when we only put HR into our study. This research result might have conflict with Chicago and Framingham studies [26, 27]. But after adopting the new index $DL = \frac{S \times HR^{0.2}}{D^{0.8}}$, the incidence of plaque formation in carotid arteries had 0.2 power positive correlation with HR. It means the increase of HR would slightly increase the incidence of plaque formation in carotid arteries.

It can be deduced that when DBP increase, the incidence of plaque formation in carotid arteries would somewhat decrease in the situation when SBP remain unchanged. When SBP and DBP remain unchanged, the decrease of incidence of plaque formation in carotid arteries could be caused by a decrease in HR [28], which was also proved by ref. [28]. In the clinical management of hypertension, we always wished to decrease the SBP and DBP in order to achieve the target BP. However, inappropriate decrease of SBP and DBP could be detrimental. Early in year 1999, Rourke and Frohlich discovered that patients with the same SBP may not have the same of incidence of CHD [28]. It has close correlation with the change of DBP. In other word the incidence of CHD has correlation with the change of both SBP and DBP. Our new index DL best explained how PP value could be used to judge the risk of plaque formation in carotid arteries quantitatively. For example, if we decrease BP of the hypertension patients from 160/90 mm Hg to 160/70 mmHg, the situation would go worse, since the DL value has been increased. If we assume that the HR remains constant, using the new index $DL = \frac{S \times HR^{0.2}}{D^{0.8}}$, the DL value would increase by 22% if we changed BP condition from $160/90^{0.8}$ to $160/70^{0.8}$. It means that after treatment, the incidence of plaque formation in carotid arteries will increase about 6% according to the results in **Figure 1**.

Our new BP index could also be used to explain the classical cases of Rourke and Frohlich [28]. In that case, they described a patient suffering from serious high DBP. They demonstrated that after reduced the BP from 188/124 mmHg to 142/64 mmHg, the patient condition became worse [28]. These phenomena could be explained by our new BP index value of *DL*. If we keep the HR unchanged, the *DL* value actually increased by after when BP decreased from 188/124 to 142/64, consequently, the incidence of plaque formation in carotid arteries would increase by 8%. These data highlight the importance of proper proportional reduction of

BP. In this case, our new BP index $DL = \frac{S \times HR^{0.2}}{D^{0.8}}$ could be used as a valuable tool to precisely calculate the correct target levels of BP in order to achieve the best effect.

In clinical practice, the incidence of plaque formation in carotid arteries is affected by multiple factors rather than by any single factor. We need to analyze how each factor affect body with all aspects considered, roundly and dynamically. The WHO has proposed that the BP should be kept to criteria of 140/90 mmHg for BP value S/D. The tendency curve in **Figure 1** may be helpful to find out the optimal proportion for SBP and DBP reduction.

In summary, the *DL* value provided a good reference in proper lowering SBP and DPB to prevent the incidence of plaque formation in carotid arteries. Since the study recruited only the elder-male-patients with arteriosclerotic, the applicability of this model in other patient populations remains to be proven by further experiments.

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