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ORIGINAL PAPER

The Role of Pulse Pressure in the Hemodynamic Control of Hypertension: Exploring the Link to Cardiovascular Remodeling

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Abstract
Objective To correlate the values in the basic blood pressure groups presented in the JNC 7th with the computed values of the Noninvasive Hemodynamic Analyzer (NHA) and to demonstrate the pathophysiological alterations by three proportional hypertensive models.
Design Hemodynamic values of each of the blood pressure groups presented in the JNC 7th are tabulated for men between 20 and 50 years of age with particular interest in Pulse Pressure.
Patients Idealized patients were used in the three groups of the proportional hypertensive models.
Validity Previous studies demonstrated that the Bias, Precision, and Accuracy of Cardiac Output measurement, compared to Thermodilution technique, resulted in statistically acceptable clinical values.
Conclusion This research has successfully demonstrated, with the use of the NHA, the leading role of Pulse Pressure in normal and hypertensive patients. We are convinced that this technique can be used as an economical and time-saving alternative screening tool in clinical medicine.

Keywords Noninvasive hemodynamic analyzer · 7th guideline for hypertension · Pulse pressure · Elderly hypertension · Hemodynamic control of hypertension

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Introduction

The use of blood pressure measurements for clinical medicine began in the United States about a century ago (Cushing 1903). It took nearly half a century for the gradual acceptance of its clinical importance. The diagnosis and management of high blood pressure has also slowly evolved. The first major steps were taken in 1960 when the correlation between blood pressure and morbidity/mortality was recognized (Freis 1960; Veteran Administration Cooperation Study 1967). Since then the emphasis on the hypertension entity increased exponentially in the United States in areas, such as, pharmacotherapy, pathophysiology, epidemiology, and nutritional & genetic aspects. During this time, a new phase in clinical medicine began with the introduction of different clinical trials. A 1948 federal research program was also initiated which produced many major discoveries in the last 50 years and, in particular, during the past 10 years. (Franklin et al. 1997, 1999, 2001; Haider et al. 2003; Mitchell et al. 2004). As a result, multiple classes of antihypertensive medications have been developed and more than 100 of them are available to the physicians today in the United States for hypertension treatment (Physician's Desk Reference, 60th ed. 2005).

Due to the U.S. Food and Drug Administration regulatory requirements, every new drug, prior to being used in patients, goes through three clinical trials (chemical, animal and human testing) with an estimated development cost per drug of about one billion dollars (Dickson and Gagnon 2004). The United States has reached the era of generally available hemodynamically effective antihypertension medications. However, as previously, patient treatment has remained trial and

error because physicians must guess the hemodynamic condition of the patient. This explains why the 7th Report of the Joint National Committee on the prevention, detection, evaluation, and treatment of high blood pressure (JNC 7th 2003) indicates that only 34% of adults between 18 and 74 years of age with hypertension have achieved blood pressure control. Thus, despite the large number of medications that have become available, the blood pressure control rates have increased only 5% in 15 years.

In the treatment of hypertension, the knowledge of the hemodynamic condition of the patient was long considered desirable, but only the basic vital signs: systolic & diastolic blood pressure and heart rate were available. The Mean Arterial Pressure (MAP) can be calculated easily, which is the geometric mean of PP and the actual opening blood pressure for the major organs. If we take the accepted maximal normal systolic and diastolic blood pressure as 140/90, the calculated MAP could be 107 mmHg (equals one third of Pulse Pressure + Diastolic Pressure). This number was practically insignificant until its role in the most important hemodynamic equation became understood:

$$[\text{MAP} - \text{CVP}] = \text{Cardiac Output [CO]} \times \text{Systemic Vascular Resistance [SVR]}$$

Because CVP is normally low, the calculation is applied in the following form:

$$\text{MAP} = \text{CO} \times \text{SVR}$$

If we are able to insert CO in the equation, the SVR can be calculated. Plotting the CO vs. SVR, the obtained square demonstrates nine different hemodynamic states with normal, low and high values. These hemodynamic parameters of hypertensive patients are of paramount importance. Since the cardiovascular system is a closed system, any change in any specific parameter of this closed system is inducing a change in the other parameters. Therefore, if we are able to accurately measure hemodynamic parameters, then we may have reached a new era of scientific progress—to treat patient etiologically and not only symptomatologically.

However, to measure CO invasively has produced insurmountable problems in the past due to the required sophisticated measuring techniques and the associated hospital expenses. As such, invasive CO measurement is generally unavailable to the hypertension population in an ambulatory setting. The introduction of noninvasive CO techniques (Sramek et al. 1996; Young et al. 2004; Ventura et al. 2005; Ferrario 2005) made the CO measurement more available for diagnosis, and treatment of hypertension.

We now introduce a novel noninvasive CO technique in this paper which may be considered a significant improvement over existing noninvasive vital sign techniques. The new technique is a computer-aided clinical decision system based on multiple algorithms involving the vital signs of a particular patient (Kabal and Lagerman 2004a). The Noninvasive Hemodynamic Analyzer (NHA) is capable of calculating the entire hemodynamic spectrum. It also provides a significant advancement in hypertension treatment because it can be directly used to conduct progressive or retrospective and ''what if?'' studies.

Our purpose in this presentation is to use the novel Noninvasive Hemodynamic Analyzer to:

(a) correlate the basic blood pressure groups according to the Seventh Report of the Joint National Committee (JNC 7th 2003) with the computed values of the NHA;
(b) calculate the hemodynamic values of each of this blood pressure groups for the 20–50 year-old male population with particular interest in Pulse Pressure; and
(c) compare our obtained hemodynamic data of three Proportional Hypertension Models to reported established pathophysiological facts of hypertension.

Methods

Our computerized clinical decision system, the NHA, is able to use any vital sign data bank independently by computing myocardial hemodynamic parameters (Kabal and Lagerman 2004a, b, 2005a, b). Considering the fact that the results of this study could not be compared to any available actual counterparts of the obtained myocardial hemodynamic parameters, but only to our calculated ideal values, the true purpose of this research was to determine the ability of the NHA to evaluate and differentiate among the reported clinical conditions with scientific objectivity. A flowchart of the NHA clinical decision system computing hemodynamic parameters is presented in Fig. 1.

The calculations are initiated with the inputs of five dynamic characteristics, namely systolic and diastolic blood pressure, heart rate, arterial oxygen saturation and hemoglobin. The two last parameters are not required for this particular study. The static characteristics of patients include date of test, date of birth, sex,

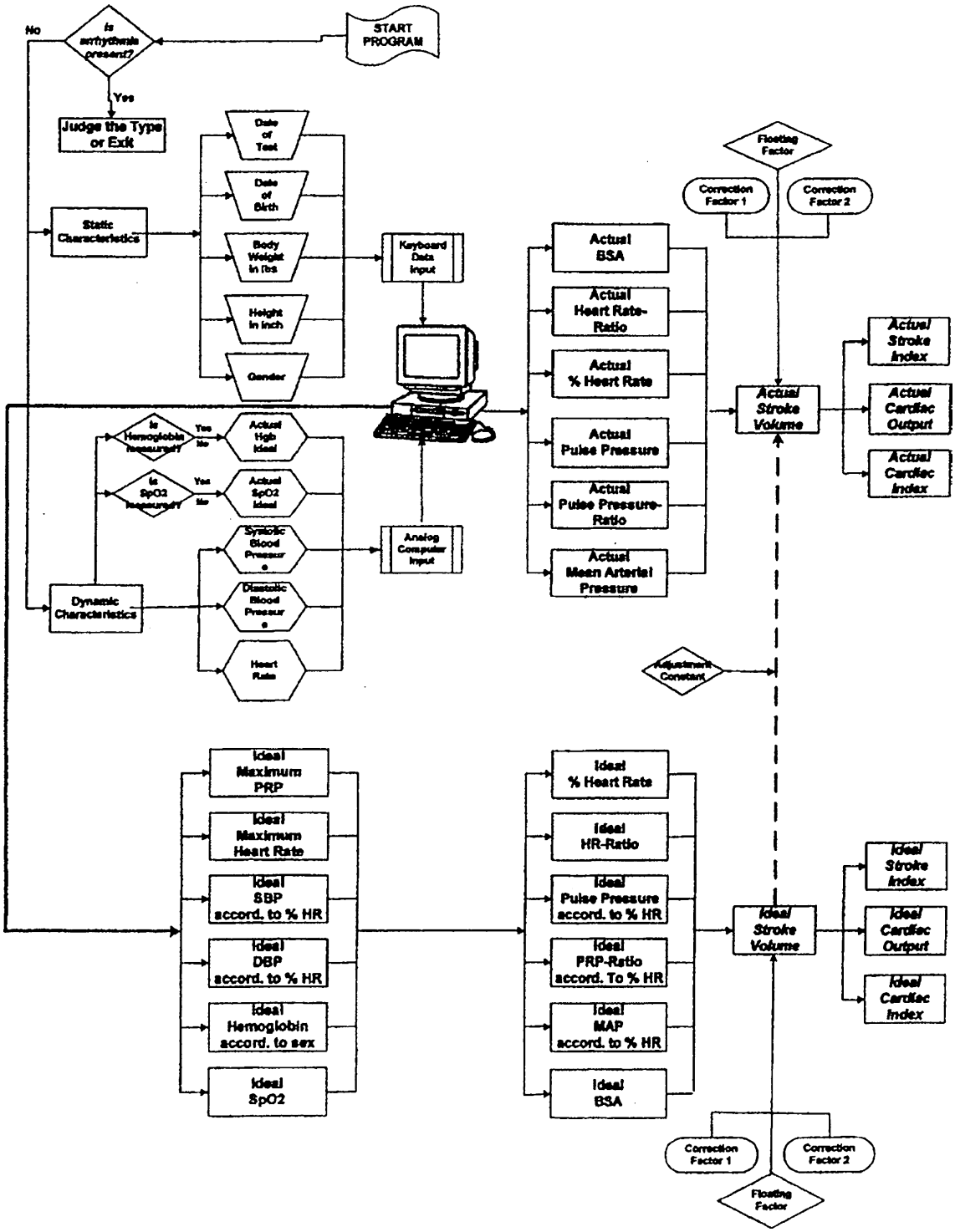

Fig. 1 Flow chart of the non invasive hemodynamic analyzer

height and body weight. The computed hemodynamic parameters are divided by the Body Surface Area (BSA), or ''indexed'' to be able to compare different patients. The software applies two algorithm cascades. Through the first algorithmic cascade, the ideal stroke volume is calculated. In the second algorithmic cascade, the actual stroke volume is computed by an adjustment constant relative to the corresponding ideal stroke volume.

The NHA software algorithm is described in detail in a recent publication (Kabal and Lagerman 2004a). It is programmed to calculate essential hemodynamic

values and, in particular, those parameters which are needed to evaluate the hemodynamic spectrum of the Left ventricle and its endocardium, as follows:

1. MEAN ARTERIAL PRESSURE (MAP): mmHg

$$MAP = ((SBP - DBP)/3) + DBP$$

It is calculated as the geometric mean of systolic and diastolic blood pressure. It represents the ''opening'' BP, which is maintained steady in a healthy person.

2. PULSE PRESSURE (PP): mmHg.

$$PP = SBP - DBP.$$

3. ENDOCARDIAL BLOOD PRESSURE (EBP): mmHg is calculated as

$$EBP = DIASTOLIC\ BLOOD\ PRESSURE - LVEDP$$

where LVEDP is LEFT VENTRICULAR END DIASTOLIC PRESSURE.

4. CARDIAC OUTPUT (CO): L/min. This most important oxygen transport related parameter describes the perfusion capability of the left ventricle. The NHA computes first the STROKE VOLUME as follows:

$$\text{square root of } ((3.14 * B * C * L) * (A/3.14 * 2) * (D/1000))$$

where A = Actual PULSE PRESSURE RATIO (PPR); PPR = Actual PULSE PRESSURE/(60/Actual HR); B = Actual HEART RATE RATIO (HRR); HRR = (60/Actual HR); C = Floating Factor as ((100 – Actual % HR) * E + F); D = Actual HR; L = E + F = Correction Factors.

5. SYSTEMIC VASCULAR RESISTANCE INDEX (SVRI): dyn.s./cm^5/m^2. A major component of afterload and its changes are inversely proportional to changes in oxygen demand.

$$SVRI = 79.92 \times (MAP - (LVEDP/2)/CI).$$

6. STROKE SYSTEMIC VASCULAR RESISTANCE INDEX (SSVRI): dyn.s.cm^5/m^2.

$$SSVRI = 79.92 \times (MAP - (LVEDP/2)/SI).$$

7. CORONARY BLOOD FLOW (CBF): ml/min/100 g. The calculation is based upon the physiological fact that the total Coronary Blood Flow is 4% of the Cardiac Output. It was calculated in the following manner:

(a) the human adult heart averages approximately 325 ± 75 g in men and 275 ± 75 g in women.
(b) the weight of the heart is correlated to the BSA. For adult normal men, the heart weight is changing between 250 and 400 g by 1.48 and 2.48 m^2 BSA scale and for women between 200 and 350 g by the scale of 1.26–2.36 m^2, respectively.

8. ENDOCARDIAL BLOOD FLOW (EBF): ml/min/100 g

$$EBF = (CBF * DIASTOLIC\ TIME\ INTERVAL)/CARDIAC\ CYCLE\ (RR)$$

9. ENDOCARDIAL RESISTANCE (ER): dyn.s.cm^5/m^2.

$$ER = 79.92 \times EBP - (LVEDP/2)/EBF).$$

10. LEFT VENTRICULAR END DIASTOLIC PRESSURE (LVEDP): mmHg was obtained by the following exponential equation as its components were also obtained noninvasively by the NHA:

$$LVEDP = (I - LCWI/A - LCWI) - (10^{0.4342944819} * LVEDI)$$

where I—LVCWI = Ideal Left Cardiac Work Index, A—LVCWI = Actual Left Cardiac Work Index, LVEDI = Left Ventricular End Diastolic Index.

At present, the invasive Swan-Ganz catheter is used directly to measure the Pulmonary End-Capillary Pressure (PECP) or Wedge Pressure. Normally, the extramural pressure (pericardial and mediastinal pressure) is negative, thus the calculated PECP values could accurately represent the true LVEDP in most of the cases.

For each actual hemodynamic parameter, the corresponding ideal hemodynamic parameters and percent differences may be computed using the same heart rate. The differences from the ideal values are considered normal within ± 20%.

Validity and limitation of the NHA Clinical Decision System

The Bias, Precision and Agreement of Cardiac Output measurements by the NHA system were compared to

the Thermodilution Cardiac Output technique with the participation of 203 ICU patients with different cardiac conditions (Kabal and Lagerman 2004a). The results of this previous retrospective study demonstrate the NHA system performs well over a wide range of CO values and within statistically accepted clinical accuracy.

The NHA clinical applications are limited to adults of both sexes over 18 years of age, provided that the input data are reliable and no significant arrhythmia is present.

Results and Discussion

Hypertension is a hemodynamic disorder, which occurs as mean blood pressure rises as the result of higher cardiac output, increased systemic vascular resistance or in combination with an abnormal hemodynamic state. Due to the effects of preliminary unknown factors, hypertension is a multilayer manifestation of a disease entity. Until pathophysiological manifestation(s) occur, we may call it essential hypertension (Carretero et al. 2000). In the United States, there are approximately sixty million hypertensive people with 95% of all hypertensive patients have Essential or Primary Hypertension.

Kaplan (2000) emphasized that more than 50% of elderly people have hypertension and the majority (75%) have Systolic Hypertension. The SBP, from approximately 55 years of age and above, presents a progressive rise parallel with decreasing DBP, producing a continuously increased PP. Most frequently these age-related changes, in a given population, occur in industrialized societies.

It is now well established that hypertension is the leading cause of morbidity/mortality of cardiovascular disease, such as, Coronary Artery Disease, Stroke and Heart Failure (de Simone et al. 1999; Kannel 2000; Psaty et al. 2001; Nair et al. 2005). Essential hypertension is masquerading with an unknown etiology and the patient remains asymptomatic for an uncertain period of time. However, as cardiovascular remodeling is taking place due to obligatory (e.g., age, gender, and genetics) or facultative factors (e.g., obesity, smoking, etc.), the consequences of essential hypertension will manifest (Pries et al. 2005; Safar 2004).

For a long time the basic hemodynamic parameters, namely SBP, DBP, MAP, PP, and HR have intrigued the scientific communities as participants in the etiology of hypertension and in its pathophysiological consequences. All these parameters are available; two of these SBP and DBP can be noninvasively measured precisely and repeatedly. Two others, PP and MAP, are derived or calculated from the two previous parameters.

The blood pressure curve is the summation of two components: (a) MAP as a steady component and (b) Pulse Pressure (PP) as a pulsatile component. In addition to the pattern of left ventricular ejection, the determinants of PP (and SBP) are the cushioning capacity (compliance) of arteries and the timing and intensity of arterial wave reflection (Sutton-Tyrell et al. 2005; Greenwald 2002). Compliance of arteries depends upon arterial volume and the elastic properties (distensibilities) of arterial walls. Compliance and distensibility are quantitative measures of the arterial wall properties (Weber et al. 2004). The term ''stiffness'' is used as an alternative to indicate qualitatively the elastic vessel wall properties (Zieman et al. 2005).

Consequently, BP is not in a steady state, but instead exhibits a dynamic nature. It is generally accepted that the normotensive blood pressure range of even healthy patients is highly variable and, therefore, an arbitrary but practical system was established. The Seventh Report of the Joint National Committee (JNC 7th 2003) on Prevention Detection, Evaluation, and Treatment of High Blood Pressure recently announced new classifications of blood pressure levels in general (Table 1) as compared to JNC 6th 1997.

The Guideline 7th is slightly modified from its earlier 6th ed. A key point to recognize is that all groups presented (normal, pre-hypertensive and to high normal levels) may exhibit normal hemodynamic levels

Table 1 Joint National Committee on Prevention Detection, Evaluation, and Treatment Guidelines for Evaluation of High Blood Pressure

Guidelines for Evaluation of High Blood Pressure			
New classification (2003)		Previous classification (1997)	
140/90 or above	High	140/90 or above	High
120–139	Prehypertension	130–139	Borderline
80–89		85–89	
		129/84 or below	Normal
119/79 or below	Normal	120–80 or below	Optimal

(normotensive & normodynamic) provided the use of an age-dependent heart rate. This fact still does not provide the etiology of progression (or stagnation) of the Guideline ranges from normal to high. Certainly when BP is over the ''high'' level, we can only surmise what is the specific level of BP where renal and/or cardiovascular remodeling starts to occur (Oparil et al. 2003; Pini et al. 2002). The first direct evidence that aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive individuals was recently reported by Dernellis et al. (2005).

The major indication of this type of grouping is that lowering the SBP (or MAP) is critically important in reducing the risk for target organ damage and clinical events (Deedwania 2002) even in the normotensive range (Izzo et al. 2000).

It is known that systolic blood pressure in industrialized countries is increasing throughout life and that diastolic blood pressure also rises continuously up to about 55 years of age (Kaplan 2000) when it levels off and begins to decreases. Prevalence of hypertension among the elderly is systolic hypertension (Chaudhry et al. 2004) due to arterial stiffness resulting in increased pulse pressure (Safar et al. 2003; Lakata and Levy 2003; Mitchell et al. 2004).

This official Guideline 7th provides general information about the normal ranges of blood pressure, but does not take into consideration the most important obligatory factors: age and gender. Using the NHA, we computed these approximate normal blood pressure ranges comparatively with the Guideline 7th between 20 and 50 year-old male population (Table 2) as follows:

Our modification of the Guideline 7th shows that the highest rise during 30-year period (20–50 years) was observed in PP as follows:

Parameters:	SBP	DBP	MAP	PP	HR
Difference:	33.3%	8.1%	19.0%	93.5%	19.0%

Since our computer-aided clinical decision system is able to compute any particular hemodynamic spectrum, if the vital signs and the anthropological values of any individual are available, we can obtain a modified and more detailed evaluation of the Guideline 7th 2003.

One of the unique properties of the NHA system is the computation of hemodynamic values from the corresponding vital signs. We selected the basic hemodynamic parameters, representing pressure, flow and resistance in three cardiac compartments, namely; (a) systemic vasculature, (b) left ventricle, and (c) endocardium of the left ventricle. The constellation of these following three parameters

$$\text{Tension} = \text{Flow} \times \text{Resistance}$$

and their derivatives express the magnitude and direction of the hemodynamic remodeling process (Table 3).

All selected subgroups are in hemodynamic equilibrium (normal physiological flow and resistance). Each value showed normal statistical difference (within $\pm$ 20%); except in the group of 50 year olds, where resistance increased 27% compared to the 20 year old value. However, here the MAP is higher and the CI is lower than in the other groups. As Table 2 showed in this subgroup, the PP was elevated 93.5% over the 20 year old. Thus, in these normal age-limited groups, PP is the most significant cardiovascular marker.

HR has shown an age-dependent decrease (– 16% between 20 and 50 year old). Meanwhile, the SI has increased 11%. The CI was statistically very close in every age group. In this total age range, the difference was only – 5%. Similarly, the left ventricle Endocardial hemodynamic reflected a normotensive, normodynamic and normovasoactive spectrum.

There is indication that the pulse pressure to stroke index ratio predict cardiovascular deterioration as the vascular stiffness increases (Fagard et al. 2001; de Simone et al. 2005). In our calculation healthy males between the ages of 20 and 50 the pulse pressure to stroke index ratio increased by 74%. Therefore, this change is also an age-dependent process in nonhypertensive patients. This ratio is a significant and independent predictor of cardiovascular events and mortality.

Years:	20	30	40	50
PP/SV	0.66	0.83	0.98	1.15

Table 2 Summary of Ideal Blood Pressure and Heart Rate according to Age, Gender (male) and Ideal Body Weight calculated by NHA

Age	Parameters				
Years	SBP	DBP	HR	PP	MAP
20	105	74	83	31	84
30	116	76	78	40	89
40	127	78	74	49	94
50	140	80	70	60	100

Table 3 Calculation of pressure, flow, and resistance in the three vascular compartments: (a) systemic vascular system (b) left ventricle and (c) left ventricle endocardium

Parameters years old	20	30	40	50
I. Systemic cardiovascular hemodynamics				
Tension	84	89	94	100
MAP mmHg	0%	6%	12%	19%
Dynamia	3.850	3.780	3.710	3.640
Cardiac Index L/min/m^2	0%	–2%	–4%	–5%
Global resistance	1661	1798	1946	2109
SVRI Dyn s/cm^5/m^2	0%	8%	17%	27%
II. Left Ventricular Hemodynamics				
Pulse pressure[a]	31	40	49	60
SBP-DBP mmHg	0%	29%	58%	94%
Ejection	47	48	50	52
Stroke index ml/min/m^2	0%	2%	6%	11%
Ejection resistance	137	141	145	148
SSVRI Dyn s/cm^5/m^2	0%	3%	6%	8%
III. Left Ventricular Endocardial Hemodynamics				
Perfusion pressure MmHg	66	68	70	72
	0%	3%	6%	9%
Endocardial blood flow	46	46	47	47
	0%	0%	2%	2%
Endocardial resistance Dyn s/cm^5	115	117	120	122
	0%	2%	4%	6%

The selected theoretical individuals are between 20 and 50 years old, 69″ in height, and in ideal weight and age-dependent heart rates, respectively. BP data were obtained from Table 2

[a] SI and SSVRI were calculated with MAP. However, PP belongs to this category only from didactic viewpoint because PP arises from the interaction of cardiac ejection (SI) and the properties of the arterial circulation

Only recently has the literature offered individual noninvasive hemodynamic evaluations. However, the Noninvasive Hemodynamic Analyzer introduces for the first time the capability of conducting ''what if?'' prognostic analysis and study. This capability may be very helpful to differentiate among physiological/pathophysiological occurrences and to observe certain events from general to specific.

In parallel with our studies, we searched for the answer to two questions? First, which hemodynamic parameter(s) are dominant in hypertension, and second, which hemodynamic parameter(s) may preferentially induce cardiovascular remodeling?

The last 10 years of hemodynamic study was especially productive in elucidating the role of PP in this aspect. Numerous reports appeared in the literature, including large double blind studies concerning selected special groups with/without hypertension and their projected hemodynamic consequences (Benetos et al. 1997, 2000; Dart and Kigwell 2001; Domanski et al. 2002).

Corroboration

Epidemiological, hemodynamic and histological studies in the last decade called the attention to PP as an independent risk factor for cardiovascular morbidity and mortality. We learned from several reports during this time that increased PP causes decreased compliance and greater stretch of arteries in the elderly. It has also been shown to cause intimal damage eventually leading to atherosclerosis with cardiovascular remodeling (Boudier 2002).

Benetos et al. (1997) has reported that a wide PP is a significant independent factor in cardiovascular mortality. They made their observations on almost 20,000 healthy men. Significant association was observed between PP and coronary, but not cerebrovascular mortality. Cerebral circulation is more dependent on SBP and several research trials proved this by observing more than 70% reduction in death from stroke (JNC 6th 1997; WHO-ISH 1999).

Moser (1999) found later, that even a decrease of BP, without achieving the maximum normal 140/90 mmHg pressure in the elderly may be beneficial to reduce coronary heart disease. The study of Blacher et al. (2000) reiterated that PP, but not MAP, determines cardiovascular risk in older hypertensive patients.

Glynn et al. (2000) agreed that PP appears to be the best predicting parameter for mortality in older people. The report of JNC7 in 2003 has included this opinion and stated that PP is an independent predictor of

myocardial infarction. The report stated that PP increases more markedly with age than does MAP.

Haider et al. (2003), focusing on blood pressure control, indicated that increased PP may help identify critical hypertensive patients earlier. Several other clinicians thought about normal PP as a therapeutic goal. For example, Safar et al (2003) indicated that future therapeutic trials using ''anti-stiffness'' medication(s) may be beneficial to decrease vascular stiffness and increased PP. Similar purpose was expressed by Safar et al. (2003), Palatini (2005) who called to our attention that the antihypertensive medication(s) should offer target organ protection.

Recent reports continue to stress the importance of PP. Panagiotakos et al. (2005) also found a close connection between PP and cardiovascular mortality in a large population of middle-aged men from various parts of the world. Assman et al. (2005) helped to understand the importance of arterial PP as a predictor of coronary heart disease risk in the clinical trial of PROCAM.

All these studies indicated and/or enforced the unique role of PP in cardiovascular pathophysiology. Recently, Mitchell et al. (2004) also suggested as a confirmation of the importance of PP that it should be a participant of the Framingham risk algorithm.

Reconciliation

In the following description, we would like to introduce three Proportional Hypertension Models of Blood Pressure Scale, which reflect the physiological/pathophysiological significance of PP and clarify the intercorrelation of Pressure, Flow and Resistance. For these theoretical representations, we selected a 50-year-old adult male with 69 in height and ideal body weight of 160 lbs.

The NHA makes it possible to compute ''what if?'' type investigations. In this series of models we reproduced three hemodynamic conditions, namely:

(1) Elderly hypertension when SBP and DBP show divergent changes. In general, at approximately 55–60 years of age, SBP begins to continuously increase and DBP decreases. The dominant hemodynamic parameter becomes the PP.
(2) Another type of elderly hypertension is the so-called Isolated Systolic Hypertension. In the second model, we demonstrate this type of Hypertension by continuously increased SBP while the DBP remained the same. In this case, the dominant hemodynamic parameter again proved to be the PP.
(3) The third model depicts a theoretical situation, when manipulating the SBP & DBP values, in that way that the PP always remained at the ideal normal level. Due to the fact that Stroke Volume calculation is based on Pulse Pressure propagation, the percent change of Blood Flow is always the same as in the case of PP.

In parallel with the obtained BP values (in particular PP changes), the corresponding cardiovascular alterations, Pressure, Flow, and Resistance, were calculated. In each cardiovascular compartment:

(a) Systemic vascular system
(b) Left ventricle, and
(c) Endocardium of left ventricle.

Our research purpose is to prove, that with the NHA, we are able to reproduce the same observations concerning the importance of PP which were obtained in various large clinical trials. The major difference is, contrary to the reported epidemiological results, we were able to present these hemodynamic alterations and immediately observe possible cardiovascular remodeling.

In Table 4, the Proportional Hypertension Model shows a classical elderly Hypertension condition where SBP & DBP, of a patient approximately 55–60 years of age, began a divergent change.

In Model (1) we changed the normal hemodynamic spectrum in such a way that SBP increased gradually with 10 mmHg pressure while DBP decreased correspondingly with 10 mmHg pressure. The maximal change was ± 40 mmHg pressure. This created an extremely high dominant PP change of 120 mmHg pressure or 100% increase over the normal basic level. However, with this hemodynamic constellation the MAP did not change.

In our Model the DBP leveled off at 60 mmHg pressure. In this case, if the pressure decreases further, this low pressure could directly compromise the perfusion pressure of the sensitive endocardium. Low DBP is really a marker for widened pulse pressure which is an indicator of increased arterial stiffness and atherosclerosis.

The maximal change in both BPs (± 40 mmHg pressure) created a characteristic Hyperdynamic, Hypovasoactive hemodynamic constellation. Along with to the 100% increase in PP, the CI and SI also increased correspondingly. Furthermore, the Endocardium of the Left Ventricle showed similar percentage increase in the Blood Flow, however, its Resistance decreased percentage wise more (– 69%)

Table 4 Proportional hypertension model [1]: Blood Pressure Scale with the corresponding cardiovascular changes Systemic vascular system Left ventricle Left ventricle endocardium

	Systemic vascular system			Left ventricle			Left ventricle endocardium		
BP	MAP	CI	SVRI	**PP**[a]	SI	SSVRI	Perfusion Pressure	BF	Resistance
180/60	100	7.280	1010	**120**	104	71	44	94	37
		100%	–52%	100%	100%	–52%	–39%	100%	–69%
170/65	100	6.370	1167	**105**	91	82	51	83	49
		75%	–45%	75%	75%	–45%	–29%	75%	–60%
160/70	100	5.460	1376	**90**	78	97	58	71	66
		50%	–35%	50%	50%	–35%	–19%	50%	–46%
150/75	100	4.550	1669	**75**	65	117	65	59	88
		25%	–21%	25%	25%	–21%	–10%	25%	–28%
Normal hemodynamic and cardiovascular spectrum									
140/80	100	3.640	2109	**60**	52	148	72	47	122
		0%	0%	0%	0%	0%	0%	0%	0%

[a] SI and SSVRI were calculated with MAP. However, PP is within this category only from a didactic viewpoint because PP arises from the interaction of cardiac ejection (SI) and the properties of the arterial circulation

All decrease or increase of the particular parameters is calculated as a percentage change of the corresponding normal values

than SVRI and SSVRI (both – 52%). Obviously, the Perfusion Pressure of the Endocardium was calculated with the lower pressure of DBP.

If we take into consideration the increased PP and these induced cardiovascular changes, which can induce cardiovascular remodeling as reported by the numerous epidemiological studies in the literature, elderly hypertension is connected with a high percentage of cardiovascular morbidity and mortality. Today, we also recognize that reduction of SBP is critically important in reducing the risk for target organ damage and clinical events.

The Proportional Hypertensive Model demonstrates a hemodynamic constellation which appears frequently in the elderly, the so-called Isolated Systolic Hypertension (Table 5).

In our Model (2) we gradually increased the SBP over the ideal values (140 mmHg) in 10 mmHg pressure increments up to maximum 180 mmHg pressure. Meanwhile, the DBP remained unchanged at the ideal level.

In this situation, the MAP showed a very moderate increase of only 13%. However, again the PP exhibited a dominating increase at the maximum SBP level of 67%. The corresponding cardiovascular consequences again demonstrated similar changes as the previous Model (1). Isolated Systolic Hypertension represents the possibility of cardiovascular remodeling leading to cardiovascular morbidity and mortality.

The Proportional Hypertensive Model (Table 6) is a hypothetical hemodynamic constellation to demonstrate the importance of PP. In this Model (3) both

Table 5 Proportional hypertension model [2]: Blood Pressure Scale with the corresponding cardiovascular changes

	Systemic vascular system			Left ventricle			Left ventricle endocardium		
BP	MAP	CI	SVRI	**PP**[a]	SI	SSVRI	Perfusion Pressure	BF	Resistance
180/80	113	6.067	1393	**100**	86	98	65	79	66
		67%	–34%	67%	67%	–34%	–10%	67%	–46%
170/80	110	5.460	1513	**90**	78	106	67	71	76
		50%	–28%	50%	50%	–28%	–7%	50%	–38%
160/80	107	4.854	1663	**80**	69	117	69	63	87
		33%	–21%	33%	33%	–21%	–5%	33%	–29%
150/80	103	4.247	1854	**70**	61	130	70	55	102
		17%	–12%	17%	17%	–12%	–2%	17%	–16%
Normal hemodynamic and cardiovascular spectrum									
140/80	100	3.640	2109	**60**	52	148	72	47	122
		0%	0%	0%	0%	0%	0%	0%	0%

[a] SI and SSVRI were calculated with MAP. However, PP is within this category only from a didactic viewpoint because PP arises from the interaction of cardiac ejection (SI) and the properties of the arterial circulation

All decrease or increase of the particular parameters is calculated as a percentage change of the corresponding normal values

Table 6 Proportional hypertension model [3]: Blood Pressure Scale with the corresponding cardiovascular changes

	Systemic vascular system			Left ventricle			Left ventricle endocardium		
BP	MAP	CI	SVRI	**PP**[a]	SI	SSVRI	Perfusion Pressure	BF	Resistance
180/120	140	3.640	2951	**60**	52	207	109	47	185
		0%	40%	0%	0%	40%	51%	0%	51%
170/110	130	3.640	2740	**60**	52	192	100	47	169
		0%	30%	0%	0%	30%	38%	0%	38%
160/100	120	3.640	2529	**60**	52	177	90	47	153
		0%	20%	0%	0%	20%	26%	0%	26%
150/90	110	3.640	2318	**60**	52	163	81	47	138
		0%	10%	0%	0%	10%	13%	0%	13%
Normal Hemodynamic and cardiovascular Spectrum									
140/80	100	3.640	2109	**60**	52	148	72	47	122
		0%	0%	0%	0%	0%	0%	0%	0%

[a] SI and SSVRI were calculated with MAP. However, PP is within this category only from a didactic viewpoint because PP arises from the interaction of cardiac ejection (SI) and the properties of the arterial circulation

All decrease or increase of the particular parameters is calculated as a percentage change of the corresponding normal values

SBP and DBP were gradually increased by 10 mmHg up to a maximum 180/120 mmHg pressure. PP remained unchanged at the level of the ideal 60 mmHg pressure.

Due to the fact that BF in the three vascular compartments is changing, as a percentage basis, in the same way as the PP (here the ideal PP was not altered), the blood flow in the Systemic Vascular System, Left Ventricle, and the Endocardium of Left Ventricle remains unchanged. We could not find any indication in the literature which stressed the significance of this percentage relationship between PP and blood flow. This fact explains that Model (3) has less indication for cardiovascular alterations than Models (1) and (2); 180/60 and 180/80 versus 180/120 mmHg pressures. Consequently, the cardiovascular remodeling in Model (3) is moderate and, therefore, it may take a longer time to deteriorate to morbidity and mortality.

Conclusions

The NHA has unique properties to compute, from vital signs, the corresponding BP range for any age (> 18 years) and gender. We recalculated the Joint National Committee Guideline 7th 2003 and found appropriate close agreement. Furthermore, we also obtained the particular cardiovascular parameters which remained normodynamic and normovasoactive in the BP ranges. It also became clear that in these gradually increasing normal ranges of BP, the PP had the most significant increase: 93.5% between 20 and 50 years of age.

In the literature, overwhelming evidence has accumulated concerning the prominence of PP. Its role and significance was stressed in hypertension in connection with cardiovascular deterioration (remodeling). Due to the fact that the NHA has the possibility for ''what if?'' studies, we investigated the leading role of PP in different hemodynamic constellations. We used three Proportional Hemodynamic Models with different BP scales. These BP scales gradual changes from the center of a 50-year old man normal BP spectrum with the corresponding three cardiovascular compartments: Systemic Vascular System, Left Ventricle and its Endocardium.

Imitating the Isolated Hypertension condition which occurs in elderly people in epidemic proportion, the PP was shown to be a dominating parameter. This particular type of hypertension is called Hyperdynamic, Hypovasoactive Hypertension because of the increased BF and low Resistance. The increased BF of the three cardiovascular compartments is dependent (in any BP constellation) on the percent PP changes because their changes in percentage are exactly the same as PP.

It became clear that at this age (50 years) the ideal PP is 60 mmHg. This PP is considered the maximum normal level. In higher ages, PP is widening due to the divergent SBP and DBP constellation. When the ideal PP is maintained by changing SBP and DBP parallel up on the scale, the serious cardiovascular consequences can be maintained at a very moderate level.

In our Proportional Hemodynamic Models, we were able to show that by increasing the PP, cardiovascular remodeling is induced. These observations are in agreement with the literature where scientific evidence has accumulated on the epidemic consequences of myocardial, brain and kidney morbidity and mortality.

Contrary to the literature, by using our Models, we were able to prove the immediate cardiovascular consequences of the different hemodynamic constellations. In the future, the NHA may offer preliminary planning possibilities for clinical trials and other research activities. Our NHA is able to compute any progressive, retrospective, and ''what if?'' studies from vital signs and anthropological data. It is capable of performing serial measurements of the patients to evaluate disease progression, responses to therapy, or any eventual interventions. Finally, the NHA is well suited to perform a wide variety of telemedicine applications.

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