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Computer-Aided Clinical Decision System: Differential Diagnosis and Treatment of Essential Hypertension by a Novel Noninvasive Hemodynamic Analyzer

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The objective of this paper was to compute cardiac output (CO) noninvasively and other hemodynamic parameters by a new computer-aided decision system: a Noninvasive Hemodynamic Analyzer (NHA), and use the obtained data to demonstrate hemodynamic instability of two hypertensive patients. The NHA is composed of several instruments, including an electronic blood pressure instrument (with pulse curve detection), oxymeter (SpO_2), hemoglobinometer and a core-body thermometer. Their data inputs are the dynamic characteristics of the patient's condition. The static characteristics including, date of birth, sex, height, weight and test date are entered manually or via computer. These inputs are analyzed by a high performance multi-function data acquisition computer. In a recently published retrospective study of 203 ICU patients thermodilution cardiac output data were compared with NHA computed CO values. Statistical evaluation, concerning bias, precision and accuracy showed clinically acceptable ranges according to a literature survey. The hemodynamic pattern of two essential hypertensive patients were computed by the NHA and diagnostic and therapeutic directions were demonstrated. The NHA computer-aided clinical decision system provides reliable guidance for hemodynamic evaluation and leads to a scientifically based differential diagnosis of hypertensive patients as a promising screening method. Since the NHA system can function separately from direct patient measurement, it can be ideally applied to telemedicine applications.

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INTRODUCTION

Hypertension (HT) remains the major risk factor involving more than fifty million Americans and its economic impact is enormous (Elliott, 2003; He and Whelton, 1997). This clinical condition is closely associated with the incidence of coronary artery disease (CAD), congestive heart failure (HF), and stroke (American Heart Association, 2002; Cushman, 2003; van den Hoogen *et al*., 2000). Unfortunately, the primary purpose of appropriate treatment of HT, namely to reach a hemodynamic equilibrium remains elusive (Sramek, 2002). This discrepancy stems from the fact that although we know the hemodynamic properties of the medication(s), we do not know the hemodynamic profile of the hypertensive patient. We can easily measure systolic and diastolic blood pressures and calculate the mean arterial pressure (MAP) which is only one side of the following hemodynamic equation:

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

where is the CVP, central venous pressure and its low value generally does not change the result of equation.

Without knowing the CO, the hemodynamic equation cannot be calculated. Thus the diagnosis and treatment of HT remains at best an approximation and/or symptomatic, but not etiologic. Therefore, in general, we want to keep the hypertension "gate" at maximum 140/90 mmHg and with clinical deduction we may judiciously use the available antihypertensive medications.

Recent introduction of other noninvasive CO techniques may reflect appropriately the hemodynamic

categories of hypertensive patients (Berton and Cholley, 2002; Newman and Callister, 1998–1999; Vidal *et al*., 2003). However, it is important to take into consideration whether the balance between a new technique and more health care dollars results in better patient treatment or remains only an "short-sighted academic interest" (Moser, 2004). This implication is not acceptable if we take into account the more then fifty million hypertensive Americans. Half of them are treated and the other half is mistreated because of the inability to identify the etiology or hemodynamic category.

Our work is an attempt to solve part of this dilemma. In this presentation we describe a clinical decision system, a novel noninvasive hemodynamic analyzer (NHA), which develop and manipulate models (simulations) of complex physiological anomalies. The NHA is able to compute CO by using patient vital signs and anthropological data as a computerized decision system. The goal to measure CO from vital signs, in particular from pulse pressure noninvasively, has not been achieved until now. The pulse contour analysis technique was introduced to measure CO by using pulse pressure. However, pulse pressure provides only relative changes in CO, therefore the measurement has to be calibrated each time to CO_{TD} (van Lieshout and Wesseling, 2001).

We overcame this challenge and avoided standardization by creating two algorithmic sequences with the input of patient vital signs and anthropological data. In the first algorithmic sequence, the proverbial fix point (the laws of levers and pulleys by Archimedes) was the physiological fact that we are able to calculate the ideal systolic, diastolic, mean arterial and pulse pressure values of an adult (>18 years old) between rest and maximum heart rate. This possibility, to be able to compute ideal pulse pressure, was the conception (and scientific basis) to obtain ideal CO at various heart rates. The actual CO was calculated by "adjusting" the difference to the ideal CO. For purposes of this research paper, we provide the reader with only a general description about this technique.

One of the important features of this new method is that retrospective analysis can be performed. If the static (body weight, height, age, gender, SaO_2 by pulse oximeter, and hemoglobin) and dynamic characteristics (SBP, DBP, HR, MAP and PP) of the patient are available to the NHA (or the program of the clinical decision system), the CO_{NHA} can be computed independently of time, place, and instrument; regardless of when the actual patient measurements were taken (Wukitsch *et al*., 1988).

The objective of this study was to apply the CO_{NHA} technique and demonstrate its feasibility in the case of two essential hypertension patients and, in particular, to diagnose their hemodynamic states and select the appropriate therapies.

ACCURACY AND LIMITATIONS OF THE CO_{NHA} TECHNIQUE

Cardiac output is the most important hemodynamic value among the parameters of hemodynamic hierarchy. Therefore, any new CO technique should be proven clinically accurate and reproducible before being applied in any clinical decision-making.

In a previous retrospective study we obtained the static and dynamic characteristics of 203 randomly selected ICU patients from the Inova Fairfax Hospital Cardiac Catheterization Laboratory located in Falls Church, Virginia (Kabal and Lagerman, 2004). The dataset contained the corresponding, simultaneously measured CO using the thermodilution technique. According to the results of the comparative statistical evaluation; bias, accuracy and precision of the CO_{NHA} technique were clinically acceptable. An applied literature survey has indicated, the CO_{NHA} technique is comparable to the accepted noninvasive techniques, such as, transesophageal doppler, bioimpedance, CO_2 rebreathing and arterial pulse contour techniques.

There are two limitations of our technique. First, it is applicable only for adults over 18-years old. Second, if arrhythmia is present, the computation will not be precise. This situation may be more prevalent at heart rates over 100 beats per minute. However, these limitations apply to all CO techniques.

METHODS

Description of the Noninvasive Hemodynamic Analyzer (NHA)

NHA applies two algorithm cascades to obtain the actual stroke volume (actual CO) and the corresponding hemodynamic profile of a particular adult patient. Through the first cascade of algorithms, the ideal stroke volume is calculated. In the second cascade of algorithms, the actual stroke volume is computed by an adjustment constant relative to the corresponding ideal stroke volume.

To calculate the ideal stroke volume of a particular patient, the following physiological correlation is utilized.

(a) Max. pressure rate product (PRP) = systolic blood pressure × heart rate/100 is plotted against the %

max. HR. It is sex dependent value; male = 333 and female = 298.
(b) Max. HR can be obtained by using regression coefficients according to age and sex.
(c) Normal HR in resting state is assumed to be 40% of max. HR
(d) From the max. ideal PRP the ideal SBP values can be calculated for any particular HR.

$$\text{PRP} = (\text{SBP} \times \text{HR})/100 \rightarrow \text{SBP}$$
$$= (\text{PRP} \times 100)/\text{HR}$$

(e) To maintain a physiologically optimal oxygenated blood supply for the vital organs, such as the brain and heart, a constant opening blood pressure is required (MAP) and this pressure is maintained by a cascade of very sophisticated biofeedback. Normal MAP is age dependent, according the scales of males: 84–100 mmHg and females: 81–97 mmHg. Considering that mean arterial pressure is the geometric average of pulse area between SBP and DBP (an approximate triangle): MAP = [(SBP − DBP)/3] + DBP
(f) DBP = MAP − [(SBP − MAP)/2]
(g) Thus through steps a to f an ideal SBP and DBP, including ideal PP can be computed according to the corresponding HR, as ideal dynamic parameters.
(h) With the above obtained dynamic and static characteristics, an ideal stroke volume (SV) can be computed by a series of equations.

The calculation of SV is based on a theoretical model of pulse wave (PW). In the aorta and/or blood vessels the manifestation of SBP as a pulse wave originates by the constriction of the left ventricle (systole). Although the values are different at the aortic level, the resulting MAP is practically the same at the cubital area where the actually blood pressure is measured.

The true SV (CO) can be measured only in the ascending aorta. However, that part of the blood volume which creates the pulse wave (PW) in the peripheral major vessels is synchronous in time (pulse rate) with the bolus of the SV. The PW is the result of the oscillation of the SBP and DBP and their difference at the largest expansion is equal to pulse pressure (PP).

If we assume that the

$$\text{PP - Ratio}\,(\text{PP} - \text{R}) = (\text{SBP} - \text{DBP}/(60/\text{HR}),$$

is essentially the circumferential change of PW $= 2r\pi$, we can calculate the area, equal to $r^2 \times \pi$, therefore

$$r = (\text{PP} - \text{R})/2 \times \pi \rightarrow [(\text{PP} - \text{R})/2\pi)^2\pi]$$

The goal in this case is to calculate the pulse wave volume (PW-V), so the approximate propagated bolus size (blood volume increase) will be equal to

$$\text{PW} - \text{V} = [(\text{PP}-R/2 \times \pi)^2 \times \pi]/(60/\text{HR})$$

Multiplying the above equation by a floating factor and taking the square root value, a so-called ideal SV is empirically computed, and divided by the basal surface area (BSA), the ideal stroke index (SI) can be obtained. Finally, multiplying both parameters with the actual heart rate, CO and/or CI are acquired. The floating factor makes it possible to have a steady CI of approximately 3.5 L/min irrespectively of age or sex. The actual SV is calculated in the same manner, but is corrected by an adjustment constant to obtain its true SV value at the actual heart rate.

The NHA is Programmed to Calculate the Following Hemodynamic Parameters as Ideal and Actual Values

1. Tension*:* Mean Arterial Pressure [MAP]: mmHg. It is calculated as the geometric mean of systolic and diastolic blood pressure. It represent the "opening" BP, which is maintained steady in a healthy person.

$$\text{MAP} = ((\text{SBP} - \text{DBP})/3) + \text{DBP}$$

2. Chronotropy: Heart rate or percentage of Max. Heart Rate

$$\%\text{of Max. Heart Rate} = (\text{Actual Heart Rate} \times 100)/$$
$$\times \text{Max. HR}$$

3. Cardiac Index (CI; L/min/m^2): This most important oxygen transport-related parameter describes the perfusion capability of the left ventricle, It is obtained as Stroke Index (SI) × Heart Rate (HR).
4. 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.

$$\text{SVRI} = 79.92 \times (\text{MAP} - (\text{LVEDP}/2))/\text{CI})$$

5. Left Cardiac Work Index (LCWI; kg/m × m^2). This value reflects the amount of physical work the left ventricle has to perform to eject CO and is proportional to the myocardial oxygen consumption.

$$\text{LCWI} = (\text{MAP} - \text{LVEDP}) \times \text{CI}) \times 0.014$$

6. Oxygen Delivery Index (DO_2I; mL/min/m^2) : Calculated as the total amount of oxygen provided by the indexed CO and is dependant upon the hemoglobin and arterial oxygen saturation (Srámek *et al*., 1995).

$$DO_2I = \text{Hemoglobin(g/dl)} \times \text{CI(L/min)} \times SpO_2 \times 1.34$$

SpO_2 represents the oxygenated hemoglobin expressed as a percentage of the hemoglobin that is capable of transporting oxygen.

The rapid hemodynamic mechanism of the left ventricle requires calculating the beat-by-beat values as follows:

7. Stroke Index (SI; mL/min/m^2): It is equivalent to the ejection performance of the left ventricle.

The NHA first computes the stroke volume as follows:

$$SV = (3.14 \times B \times C \times L)^{1/2} \times (A/3.14 \times 2) \times (D/1000)$$

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; L = Adjustment Constant; D = Actual HR; E + F = Correction Factors.

8. Stroke Systemic Vascular Resistance Index (SSVRI; dyn. s. cm^5/m^2): It represents the major component of the afterload of the left ventricular function.

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

9. LV End Diastolic Index (LVEDI; mL/m^2) It is a representative value for the systemic volemic state.

$$LVEDI = (SV/(\%EF/100))/BSA$$

BSA = Basal Surface Area

10. LV Efficiency Ratio or Ejection Fraction (% EF): The pumping efficiency of the left ventricle; more specifically, it represents the percentage of blood volume ejected from the left ventricle during systole.

In the first step, an ideal EF is calculated and adjusted to HR according to

$$\text{Ideal \% EF} = ((\text{Actual \% HR} - 40) \times 0.1) + 57$$

where Actual % HR = (HR × 100)/Max. HR

$$57 = \text{theoretical average \% EF}$$

In the second step, the Actual % EF is calculated, according to:

$$\text{Actual \% EF} = \frac{(PP - A \times HR - A)}{(PP - I \times HR - I)} \% \text{ EF} - 1$$

11. LV End Diastolic Pressure (LVEDP; mmHg): This parameter was obtained by the following exponential equation using the NHA:

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

I-LCWI = Ideal Left Cardiac Work Index; A-LCWI = Actual Left Cardiac Work Index; LVEDI = Left Ventricular End Diastolic Index.

12. LV Stroke Work Index (LVSWI; g m/m^2): Representing the amount of physical work the left ventricle has to perform to eject the SV and is proportional to the myocardial oxygen consumption.

$$LVSWI = (MAP - LVEDP) \times SI \times 0.0144$$

13. Acceleration Index (ACI; s^{-2}): This value reflects the peak acceleration of blood after opening of aortic valve, reflecting myocordial contractility (Inotropy).

$$ACI = \sqrt{((PP - R \times 20)/HR - Ratio)/1000} \times \text{Factor}$$

14. Pulse Pressure (PP; mmHg) It represents the difference of SBP and DBP which is equivalent with propagation of left ventricular contraction (stroke) in the blood vessels.

A flowchart of the NHA clinical decision system computing CO and multiple hemodynamic parameters is represented in Fig. 1. This schematic presentation is only intended to provide a general idea about the computation of the CO_{NHA} approach.

APPLICATION OF NHA METHOD

Two hypertensive patients were evaluated by the guidelines of the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (Amsterdam, 2003; Chobanian *et al*., 2003). Diagnosis of hypertension was based on

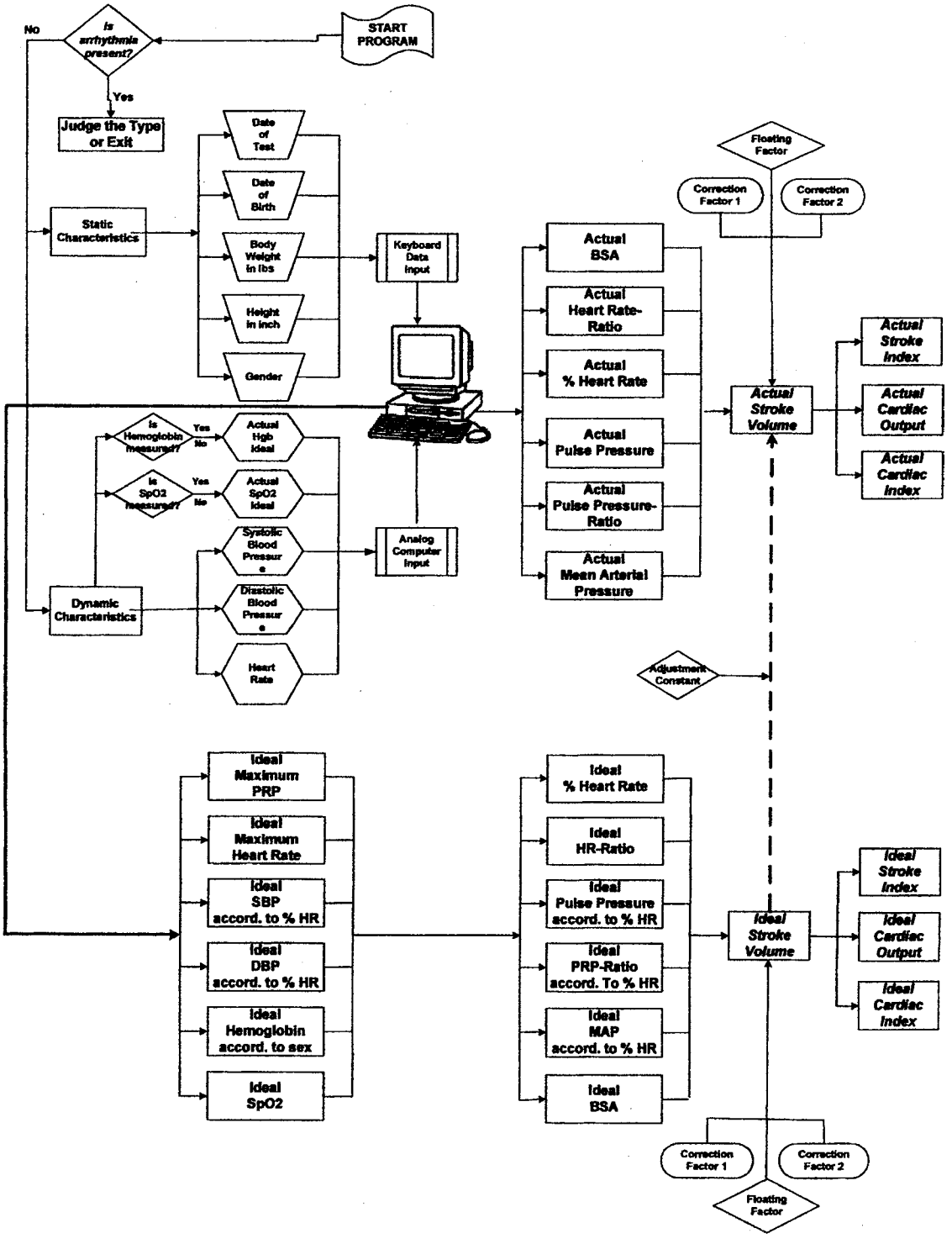

Figure 1. Cardiovascular clinical decision system: Flowchart of the noninvasive hemodynamic analyzer (NHA).

three consecutive elevated blood pressure readings with two readings measured at each visit on both arms. Blood pressure was measured with a correctly sized cuff after the patient had rested in a quiet room for 10 min.

CLINICAL CASE 1

This patient is a 43-year-old White married female and a mother of two teenage girls. She works as a saleswoman. Recently she became more tired after an 8-h workday and complains about frequent mild headaches. She usually sleeps 8 h, but does not feel rested in the morning. Her last physical examination was 5 years ago. Her ECG was normal and except for a long history of mildly elevated cholesterol, the previous Comparative Metabolic Profile and CBC were WNL. The patient had a complete hysterectomy 5 years ago. She has never had cardiovascular diseases or diabetes. She does not have any stressful conditions in her family or social life. Her mother is obese, free of diabetes and cardiovascular diseases. Her father died of a stroke at age of 52 after a long history of hypertension.

Her height is 167 cm, body weight is 85 kg with moderately increased body frame. Her body mass index is 32. She is nonsmoker and nondrinker. She gradually gained 16 kg after her hysterectomy. She is on her feet all day, but after work is practically sedentary.

Physical examination reveals the appearance of a moderately obese, middle-aged female in good mood. She has no pathological finding, except moderate bilateral ankle and knee discomfort. No carotid bruits, murmurs, left ventricular hypertrophy or jugular filling at 90°. Bilateral blood pressure readings are satisfactorily close. Measurements were taken after a 10-min resting period. Blood pressure in supine was 164/78 and in upright 168/83 with 73/79 heart rate, respectively. Very similar measurements were obtained previously in three consecutive periods of 1 month. Respiratory rate was 16/min, temperature was 97.6°F, and arterial oxygen saturation (SpO_2) was 97%.

Laboratory Tests: CBC was WNL with 13.2 g/dL of hemoglobin. Comparative Metabolic Profile was essentially WNL. Cholesterol was 212 mg/dL, HDL-Cholesterol was 68 mg/dL and LDL-Cholesterol was 110 mg/dL with Cardiac Risk Ratio of 3.1. U/A was unremarkable. The 12-lead ECG shows normal sinus rhythm. The patient is on Premarin since her hysterectomy and is taking Advil occasionally.

Table 1 presents the patient's ideal and actual parameters with the calculated percent differences. The conventional diagnosis is primary or essential hypertension because she does not have any known pathophysiological condition. The clinical significance of the NHA system is that differential diagnosis can be made by its computed hemodynamic parameters. Diagnostic decisions are reflected on the conventionally accepted normal physiological ranges. Actual values compared to the ideal values and their differences are expressed in percentage. Ideal values are calculated with the same heart rate as the corresponding actual value groups. This computerized clinical decision system is providing information not only about the systemic, but also the local or the left ventricular hemodynamic interactions.

Stroke Volume or Ejection Load is dependent on three intricately linked factors:

1. Preload
2. Myocardial Contractility
3. Afterload

Preload is the left ventricular end diastolic index and designates the volume force distending the left ventricle. The greater the extension of the left ventricle, the greater the force of contraction. Afterload or stroke vascular resistance is the force against which the left ventricle ejects blood during systole and generates aortic blood pressure. The myocardial contractility is the intrinsic ability of the myocardial fiber to produce peak tension of force in the first seconds of systolic constriction (inotropy). This force is independent from the major part of ventricle contraction which is under the influence of preload and afterload. The direction of myocardial contractility is changing parallel with the increase/decrease of stroke index.

This computerized clinical decision system is able to differentiate between systemic and/or pulmonary volume overload. Preload or left ventricular end diastolic index provides insight about systemic volume load, except in valvular incompetence. The left ventricular end diastolic pressure represents the left ventricular filling pressure which, in general, reflects the pulmonary wedge pressure.

In this particular situation (Fig. 2) SI increased with 54.2/48.3% over the calculated ideal values while the inotropy increased with 24.2/17%, respectively. In the same time, stroke vascular resistance decreased with −27.4/−21.2%. This hemodynamic constellation demonstrates a left ventricular hyperdynamic condition.

By graphically presenting the patient's systemic hemodynamic profile, the possibility arises not only for differential diagnosis, but the appropriate selection of medication(s).

Figure 3 demonstrates the global hemodynamic interaction by depicting MAP against the CI. The diagonal straight lines shows the ideal range of SVRI where the upper line corresponds with vasodilatation and the lower line with vasoconstriction. The curved lines give

Table 1. Diagnostic Directions of Hemodynamic Analysis—Clinical Case 1

Parameters	Normal physiological ranges	Supine position				Upright position			
		Ideal	Actual	Differences (%)	Diagnoses	Ideal	Actual	Differences (%)	Diagnoses
Tension									
Mean arterial blood pressure: MAP	84–100 (mmHg)	93	107	14.7	Hypertension	93	111	19.7	Hypertension
Dynamia									
Cardiac index: CI	2.8–4.2 (L/min/m^2)	3.4	5.3	54.2	Hyperdynamia	3.9	5.8	48.3	Hyperdynamia
Afterload: SVRI									
Syst. vasc. resist.	1660–2580 (kg/m m^2)	2.073	1.506	−27.4	Hypovasoactivity	1.810	1.427	−21.2	Hypovasoactivity
Mycord O_2 consump.									
Left cardiac work index: LCWI	3.3–5.3 (kg/m m^2)	4.2	7.1	68.5	Hyperactivity	4.8	8.1	68.8	Hyperactivity
Total O_2 Delivery									
Oxygen delivery index: DO2I	480–670 (mL/min/m^2)	565	911	61.2	Hyper-O_2-Delivery	644	997	54.9	Hyper-O_2-delivery
Chronotropy									
Heart type and/or % max. heart rate	37–43 (% of Max. HR)	40	40	0.0	Normochronotropy	44	44	0.0	Hyperchronotropy
Ejection load									
Stroke index: SI	30–65 (mL/min/m^2)	47	73	54.2	Hyperjection	50	74	48.3	Hyperjection
Ejection resistance									
Stroke syst. vasc. resist. Index: SSVRI	109–237 (dyn. s/cm^5/m^2)	151	110	−27.4	Normo-S-vasoact.	143	113	−21.2	Normo-S-vasoact.
Preload = volemia									
End diastolic index: EDI	60–110 (mL/min/m^2)	82	102	24.2	Normovolemia	86	109	26.7	Normovolemia
Efficiency ratio (LV)									
Ejection fraction: % EF	50–65 (%)	58	71	24.2	Hyperefficiency	58	68	17	Hyperefficiency
LV filling pressure									
Pulmonary wedge pressure: LVEDP	4–12 (mmHg)	7	13	76.8	Hyperpulmovolemia	9	15	77.4	Hyperpulmovolemia
Inotropy									
Acceleration index: ACI	0.9–1.7 (s^2)	1.3	2.6	24.2	Hyperinotrpy	1.5	1.8	17.0	Hyperinotropy
Ejection work									
LV stroke work index: LVSWI	36.7–79.6 (g m/m^2)	67.4	97.9	45.3	Hyper-S-capacity	60.4	102.0	68.8	Hyper-S-capacity
Pulse pressure									
S-D arterial pressure difference: PP	25–55 (mmHg)	56	86	54.2	Hyperkinetic-pulse	62	85	37.0	Hyperkinetic-pulse

Note. Diagnostic decision are reflected on the conventionally accepted normal physiological ranges. Actual values are also compared to the ideal values and their differences are expressed in percent. Ideal values are calculated with the same heart rate as the corresponding actual groups.

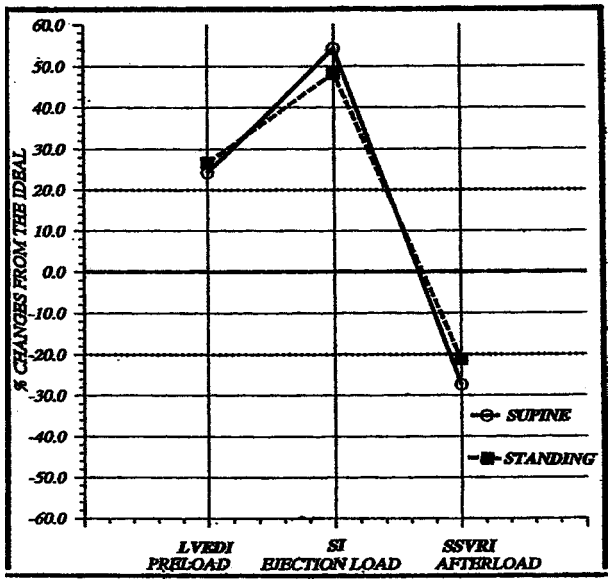

Figure 2. Left ventricular hemodynamic interactions of patient 1.

the ideal range of the LCWI. According to the increased MAP and CI, the differential diagnosis is hyperdynamic hypertension with compensatory vasodilatation or hypovasoactivity. The increased cardiac output is due to hyper-ejection because the heart rate is within normal limits. In this hyperdynamic condition the LCWI is also significantly elevated.

When the ideal high- and low-normal CI levels are depicted against the different hemoglobin values (with the average normal SpO_2), a continuous ideal lower and upper normal level of DO_2I can be calculated. Accordingly, above the upper line, oxygen supply and under the lower line oxygen demand can be observed (Fig. 4).

This patient exhibits hyperdynamia, normal SpO_2 and adequate hemoglobin level, which results in a high oxygen delivery index, positioned over the calculated ideal maximal normal range of DO_2I in the oxygen supply side. In the lower right corner, the oxyhemoglobin dissociation curve demonstrates that 97% oxygen saturation corresponds with 100 mmHg PaO_2.

According to her isolated systolic hypertension, she has Stage 2 hypertension, which places her in Risk Group C, indicating immediate therapeutic intervention. This hemodynamic constellation indicates the use of a beta-blocking agent with a mild diuretic. The patient was also advised to have controlled weight-reduction with an appropriate diet program as an alternative approach to blood pressure control. In the following weeks a trending curve was obtained until normal BP was reached.

CLINICAL CASE 2

Patient is a 37-year-old Afro-American male truck driver, who complains about occasional headaches and sometimes feels slightly dizzy in the morning. He had normal physical examination about 2 years ago. No history of hospitalization or chronic health problems. He was divorced 3 years ago and lives alone. Smokes one pack of cigarettes a day and is a moderate, but steady beer drinker. He used to do garden work, but is generally tired after frequent night driving. His blood pressure was found high in recent months.

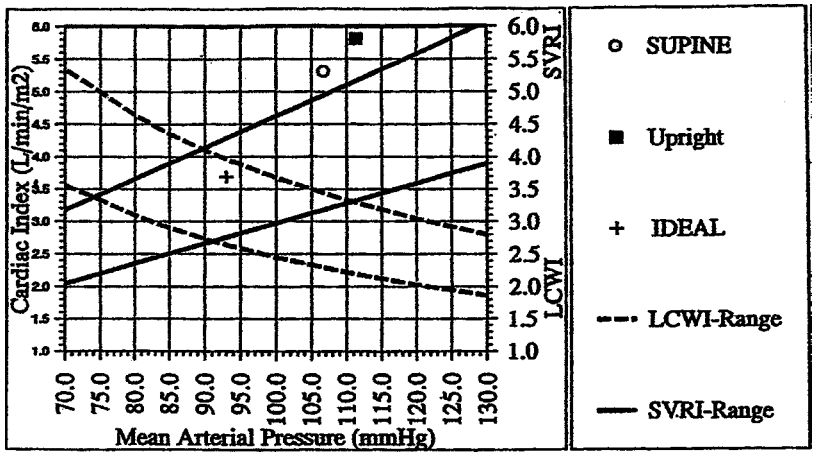

Figure 3. Global hemodynamic interactions of patient 1. In supine and standing. Hemodynamic status: 1. Hypertensions (MAP). 2. Hyperdynamia (CI). 3. Hypovasoactivity (SVRI). 4. Hypercapacity (LCWI).

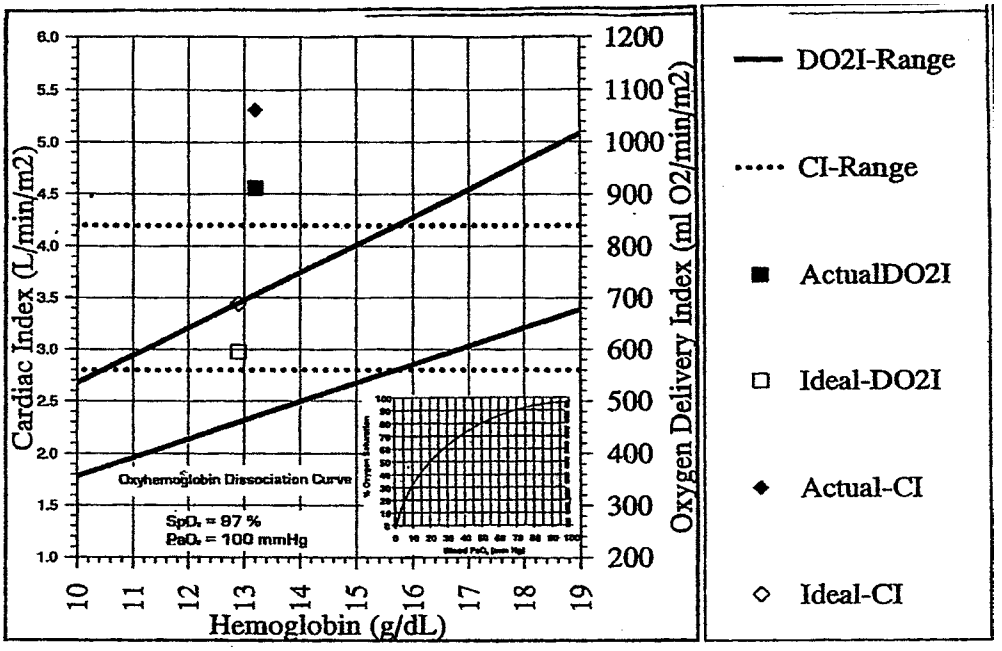

Figure 4. Oxygen supply/demand and Oxygen Delivery Index—Patient 1. The presented range of Oxygen Delivery Index was calculated by relating the normal range of Cardiac Index (2.8–4.2 L/min/m^2) to the particular value of Hemoglobin. The area of upper straight line: Oxygen supply under the lower straight line: Oxygen demand.

Physical examination was essentially normal. He was moderately overweight. His height is 178 cm, body weight of 92.5 kg with medium/large frame. Fundoscopic examination was normal. Cardiovascular examination was WNL. Bilateral jugulars were not filled at 90°, no carotid bruits or murmurs. His chest was clear on percussion and auscultation. Central and peripheral reflexes were normal. Romberg sign is negative. Blood pressure measurements were same in left and right cubital areas. Blood pressure in supine was 152/105 and in upright 154/112 mmHg. Heart rates 68/75. Measurements were taken after 10 min resting periods.

Arterial O_2 saturation (SpO_2) was 93%, hemoglobin was 16.1 g/dL, CBC and U/A are unremarkable. SMC-24: Cholesterol was 232 mg/dL, HDL-Cholesterol was 38 mg/dL and LDL-Cholesterol is 155 mg/dL with an elevated Cardiovascular Risk of 6.1. The remaining chemistry is WNL, with the exception of GGT which is mildly increased. His ECG revealed sinus rhythm and borderline left ventricular hypertrophy.

According the patient history and physical evaluation, the conventional diagnosis is primary or essential hypertension (Table 2). The NHA is able to compute both the left ventricle and systemic hemodynamic condition. The left ventricular hemodynamic constellation clearly indicates increased stroke vascular resistance compared to the calculated ideal values. However, these changes were not outside the normal physiological ranges (Fig. 5).

The systemic hemodynamics of the second patient is manifested with a moderately increased systemic vascular resistance index and a normal cardiac index. Therefore, the differential diagnosis is hypervasoactive-normodynamic hypertension (Fig. 6).

The normal CI is the result of the normal SI with a normal heart rate. Although the CI is still in the normal range (with normal hemoglobin and slightly decreased SaO_2), there is a decreased oxygen delivery index, but remained above oxygen demand. The decreased SaO_2 resulted in a considerable decrease to 80% of PaO_2 (Fig. 7).

This patient belongs to Stage 2, Risk Group C of primary or essential hypertension. The Seventh Report of the Joint National Committee recommends that hypertensive patients with this classification should be treated immediately. This hemodynamic constellation requires using of a calcium channel blocking agent (Hall *et al.*, 1998) combined with an ACE-Inhibitor. Due to his elevated cardiovascular risk factors with an increased cholesterol level, the patient also began taking Lipitor 20 mg daily.

Table 2. Diagnostic Directions of Hemodynamic Analysis—Clinical Case 2

Parameters	Normal physiological ranges	Supine position				Upright position			
		Ideal	Actual	Differences (%)	Diagnoses	Ideal	Actual	Differences (%)	Diagnoses
Tension									
Mean arterial blood pressure: MAP	84–10 (mmHg)	93	121	30.1	Hypertension	93	126	35.9	Hypertension
Dynamia									
Cardiac index: CI	2.8–4.2 (L/min/m^2)	3.5	3.5	1.1	Normodynamia	3.2	3.2	−0.3	Normodynamia
Afterload: SVRI									
Syst. vasc. resist.	1660–2580 (kg/m m^2)	2.058	2.646	28.6	Hypervasoactivity	2.218	3.024	36.3	Hypervasoactivity
Mycord O_2 consump.									
Left cardiac work index: LCWI	3.3–5.3 (kg/m m^2)	4.2	5.6	31.5	Hyperactivity	4.0	5.4	35.5	Hyperactivity
Total O_2 Delivery									
Oxygen delivery index: DO2I	570–795 (mL/min/m^2)	673	702	4.2	Normo-O_2-delivery	627	643	2.7	Normo-O_2-delivery
Chronotropy									
Heart type and/or % max. heart rate	37–43 (% of Max. HR)	36	36	0.0	Hypochronotropy	40	40	0.0	Normochronotropy
Ejection load									
Stroke index: SI	30–65 (mL/min/m^2)	51	51	1.1	Normoejection	43	43	−0.3	Normoejection
Ejection resistance									
Stroke syst. vasc. resist. Index: SSVRI	109–237 (dyn. s/cm^5/m^2)	140	180	28.6	Normo-S-vasoact.	166	227	36.3	Hyper-S-vasoact.
Preload = volemia									
End diastolic index: EDI	60–110 (mL/min/m^2)	89	90	0.6	Normovolemia	75	78	4.9	Normovolemia
Efficiency ratio (LV)									
Ejection fraction: % EF	50–65 (%)	57	57	0.6	Normoefficiency	57	55	−4.9	Normoefficiency
LV filling pressure									
Pulmonary wedge pressure: LVEDP	4–12 (mmHg)	7	10	31.6	Normopulmovolemia	7	9	35.5	Normopulmovolemia
Inotropy									
Acceleration index: ACI	0.7–1.5 (s^2)	1.0	1.0	0.6	Normoinotrpy	1.1	1.0	−4.9	Normoinotrpy
Ejection work									
LV stroke work index: LVSWI	36.7–79.3 (g m/m^2)	82.9	82.1	−1.0	Hyper-S-capacity	53.0	71.8	35.5	Normo-S-capacity
Pulse pressure									
S-D arterial pressure difference: PP	25–55 (mmHg)	46	47	1.1	Normokinetic-pulse	46	42	−9.6	Normokinetic-pulse

Note. Diagnostic decision are reflected on the conventionally accepted normal physiological ranges. Actual values are also compared to the ideal values and their differences are expressed in percent. Ideal values are calculated with teh same heart rate as the corresponding actual groups.

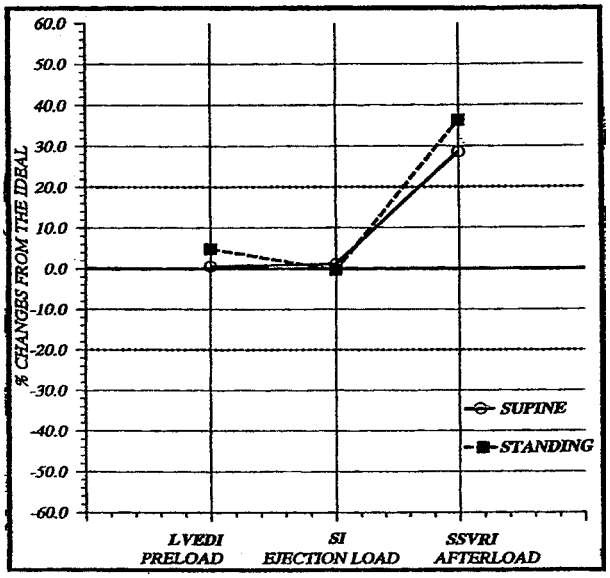

Figure 5. Left ventricular hemodynamic interactions of patient 2.

Hemodynamic trending (the arrow indicates the desired direction) during normalization of BP was followed and his maintenance dose was appropriately adjusted.

DISCUSSION

The critical importance of cardiac output to properly diagnose and treat cardiovascular problems has made it a primary research target. Once CO is known, a whole sequence of hemodynamic parameters can be calculated. The hospital-based invasive thermodilution technique is frequently challenged by new noninvasive CO techniques. Although they have not reached the same level of accuracy, thus far not one noninvasive technique has taken the place of the complicated, expensive, and sometimes life-threatening thermodilution technique (Bernard *et al.*, 2000). According to our previous study, the CO_{NHA} technique favorable compares with these noninvasive CO techniques, in which the statistical evaluation showed similar range of bias, accuracy and precision compared to CO_{TD}.

The most important role of CO in the hemodynamic hierarchy is to regulate blood flow and pressure distribution by an integrated function and thereby maintain an adequate oxygen transport at the organ/cellular level (Marlow, 2002; Shoemaker *et al.,* 1999). The key position of oxygen transport in various clinical conditions makes it critical to measure the cascade of hemodynamic balance. But without knowing the CO/CI, these hemodynamic parameters cannot be obtained. If CI is known, we are able to calculate alongside with the major hemodynamic parameters, the oxygen delivery index (with the corresponding SpO_2 and hemoglobin values).

Pulse oxymetry measurement (Lynn-MacHale and Crison, 2004) reflects the percentage of hemoglobin that is capable of transporting oxygen in the blood. This estimate of hemoglobin saturation is called SaO_2. The relationship between the "arterial" oxygen saturation and partial pressure of oxygen in arterial blood (PaO_2) is not linear, but rather it results in an S-shaped curve (Wukitsch *et al.*, 1988). As a practical rule shows 90, 60, and 30 SaO_2 corresponds with 70, 30, and 10 PaO_2, respectively. Therefore, when the PaO_2 is high, the oxygen binds with hemoglobin and releases it at a low PaO_2. This is the basis of normal

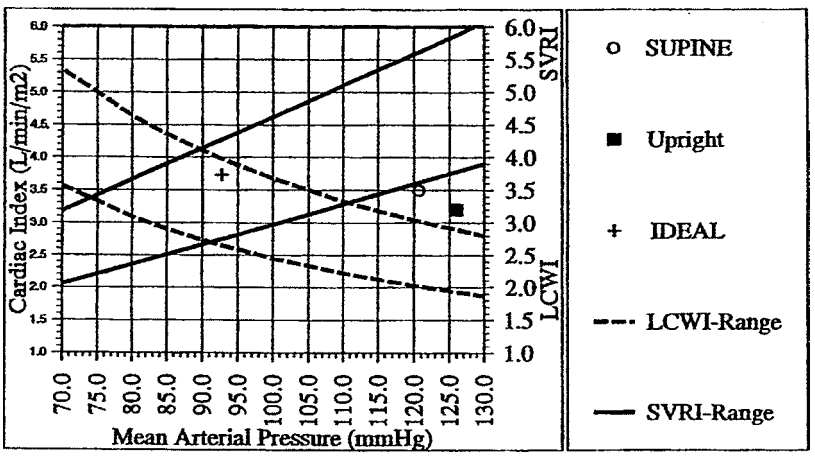

Figure 6. Global Hemodynamic interactions of patient 2. In supine and standing. Hemodynamic status: 1. Hypertension (MAP). 2. Normodynamia (CI). 3. Hypervasoactivity (SVRI). 4. Hypercapacity (LCWI).

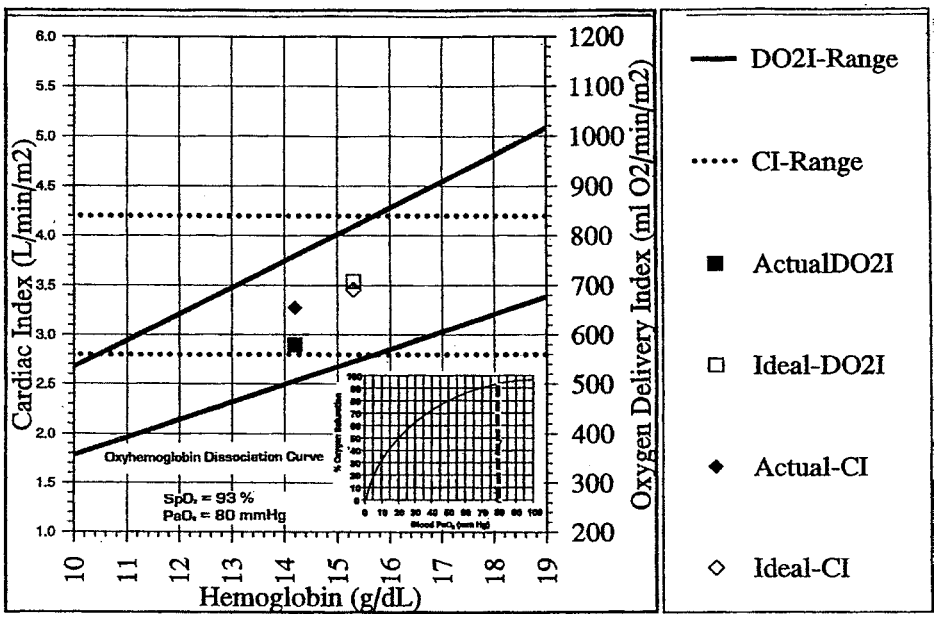

Figure 7. Oxygen Supply/demand and Oxygen Delivery Index of patient 2. The presented range of Oxygen Delivery Index was calculated by relating the normal range of Cardiac Index (2.8–4.2 L/min/m^2) to the particular value of Hemoglobin. The area of upper straight line: Oxygen supply under the lower straight line: Oxygen demand.

oxygen transport. Accordingly, the first patient had 97% arterial O_2 saturation, which corresponds with 100 mmHg of blood PaO_2. However, the second patient had a relatively small change, namely 93% arterial O_2 saturation, which represented a significant shift downward to 80% of PaO_2.

The determination of oxygen supply/demand by calculating DO_2I is able to identify conditions, (e.g., CAD, HF, etc.) in an ambulatory setting. The NHA can also be applied invasively where it can be useful in operative and post-operative situations.

The Two Presented Cases Demonstrate the Clinical Applicability of NHA in Hypertension Disease

1. *Differential diagnosis* is achieved essentially by obtaining both sides of the hemodynamic equation:

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

Since the MAP can be elevated by the combination of Flow × Resistance, the etiology in essential hypertension is scientifically achieved and the diagnosis of normo-, hyper- or hypodynamic and/or normo-, hyper-, or hypovasoactivity precisely can be established.

2. *Treatment* by (a) matching the medication'(s) hemodynamic properties with the actual hemodynamic profile of the patient, and (b) selecting effective medication(s) which fits the patient's recognized qualitative risk factor(s).

In Clinical Case 1, the patient is hyperdynamic and treated with cardioselective beta-blocking agent and minimal diuretic.

The second patient in Clinical Case 2 is an African American man. African American's have more severe forms of hypertension due to end-organ damage and treatment/compliance is more difficult (Lackland and Keil, 1996; Jamerson, 2000). According to the hypertension-literature, the African American patients more frequently have low-renin, high-volume hypertension (Materson *et al.*, 1993). Figure 6 shows a hemodynamic constellation which requires a combined dose of a calcium channel blocker and an ACE-Inhibitor. This is in agreement with recent reports that in most of the cases, African American patients respond better to calcium channel blockers. However, they may also respond to blockers of the renin–angiotensin–aldosterone system (RAAS), but less than other patients.

3. Trending [Follow-up] as needed for fine tuning of the treatment(s); the graphical presentation-interface covers every major aspect of the hemodynamic changes by which treatment is easily determined. Thus, the obtained hemodynamic profile together with the physician clinical

judgment offers new possibilities in the differential diagnosis of hypertension disease.

This computer-aided clinical decision system has the potential of appropriate continuity which is important to trend progress in the disease process or following of treatment(s). Its application does not require any unique training for data collection/standardization and does not cause any safety risk to the patient. This noninvasive technique is easily altered to an invasive approach which is unprecedented among the other methods (Velmahos *et al*., 2000). Without any restriction, it can be used in any environment from ambulatory office settings to the operating room. From the viewpoint of healthcare, the use of NHA method is very inexpensive.

In patient care and research, this novel noninvasive hemodynamic analyzer will help us recognize that hypertension is more than just blood pressure control. The current therapeutic goal should also include normodynamia and normoperfusion with normal oxygen delivery. Knowing the hemodynamic background of essential hypertension, we are able to better understand the physiological and/or pathophysiological interconnections.

CONCLUSION

1. The NHA technique may be used as a screening device to determine the hemodynamic interactions of essential hypertension.
2. Obtaining oxygen supply/demand by computing DO_2I, could identify conditions (e.g. CAD, HF, etc.) in ambulatory settings.
3. The NHA can also be used invasively in operative and post-operative situations to display a continuous real-time hemodynamic trend recognizing acute circulatory dysfunction.
4. The vital signs collection from the patient can be independent from the use of the NHA. Therefore, this method can be applied ideally to telemedicine applications.

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REFERENCES

American Heart Association. *Heart Disease and Stroke statistics-2003 Update*. Dallas, TX: American Heart Association, 2002.

Amsterdam EA. JNC 7: A moving guideline responds to a moving target (editorial). *Prev Cardiol* 6: 177–178, 2003.

Bernard GR, Sopko G, Cerra F, Demling R, Edmunds H, Kaplan S, Kessler L, Masur H, Parsons P, Shure D, Webb E, Weidemann H, Weinmann G, and Williams. Pulmonary artery catheterization and clinical outcomes: National Heart, Lung, and Blood Institute and Food and Drug Administration Workshop Report. Consensus Statement. *JAMA* 283(19): 2577–2578, 2000.

Berton C, and Cholley B. Equipment review: New techniques for cardiac output measurement—oesophageal Doppler, Fick principle using carbon dioxide, and pulse contour analysis. *Crit Care* 6(3): 216–221, 2002.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, and Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA* 289(19): 2560–2572, 2003.

Cushman WC. The burden of uncontrolled hypertension. Morbidity and mortality associated with disease progression. *J Clin Hypertens* (3 Suppl 2): 14–22, 2003.

Elliott WJ. The economic impact of hypertension. *J Clin Hypertens* 5(3 Suppl 2): 3–13, 2003.

Hall WD, Reed JW, Flack JM, Yunis C, and Preisser J. Comparison of the efficacy of dihydropyridine calcium channel blockers in African American patients with hypertension. *Archives of Internal Medicine* 158: 2029: 2034, 1998.

He J, and Whelton PK. Epidemiology and prevention of hypertension. *Med Clin North Am* 81(5): 1077–1097, 1997.

Jamerson KA. Rationale for angiotensin II receptor blockers in patients with low-renin hypertension. *Am J Kidney Dis* 36(3 Suppl 1): 524–530, 2000.

Kabal J, and Lagerman BK. A novel approach to measure cardiac output noninvasively: A comparison with the thermodilution method on critical care patients. *J. Clin Monit* 18(3): 189–197, 2004.

Lackland DT, and Keil JE. Epidemiology of hypertension in African Americans *Semin Nephrol* 16(2): 63–70, 1996.

Lynn-MacHale DJ, and Crison KK. (Eds.). *AACN Procedure Manual for Critical Care,* 4th ed. Pennsylvania: W.B. Saunders.

Marlow G. Deficient oxygen transport: An alternative mechanism for the development of hypertension? *Am J Hypertens* 15(10 Pt 1): 924, 2002.

Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, Hamburger RJ, Fye C, Lakshman R, and Gottdiener J. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *N Eng J Med*. 328: 914–921, 1993.

Moser M. Keep the management of hypertension simple. *J Clin Hypertens* 6(3): 113–115, 2004.

Newman DG, and Callister R. The noninvasive assessment of stroke volume and cardiac output by impedance cardiography: A review. *Aviat Space Environ Med* 14/70(8): 780–789, 1999–1998.

Shoemaker WC, Thangathurai D, Wo CC, Kuchta K, Canas M, Sullivan MJ, Farlo J, Roffey P, Zellman V, Katz RL. Intraoperative evaluation of tissue perfusion in high-risk patient by invasive and noninvasive hemodynamic monitoring. *Crit Care Med* 27(10): 2147–2152, 1999.

Srámek BB. *Systemic Hemodynamics and Hemodynamic Management. Medical Textbook*. Collierville, TN: Instantpublisher.Com, 2002.

Srámek BB, Valenta J, and Klime F (Eds.). *Biomechanics of the Cardiovascular System*. Czech Technical Univ. Press. Prague, Czech Republic, 1995, pp. 209–231.

Van den Hoogen PCW, Feskens EJM, Nagelkerke NJD, Menotti A, Nissinen A, and Kromhout D. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. *N Eng J Med* 342(1): 1–8, 2000.

van Lieshout JJ, and Wesseling KH. Continuous cardiac output by pulse contour analysis: Editorial. *Brit J Anaest* 86(4): 467–468, 2001.

Velmahos GC, Demetriades D, Shoemaker WC, Chan LS, Tatevossian R, Wo CC, Vassiliu P, Cornwell EE 3rd, Murray JA, Roth B, Belzberg H, Asensio JA, and Berne TV. Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. *Ann Surg* 232(3): 409–418, 2000.

Vidal AER, Cerón DU, and Siere UA. Agreement between two methods for cardiac output determination in critically ill patients: Transesophageal Doppler and Bolus Thermodilution. *Rev Assoc Mex Med Crit Ter Int* 17(2): 44–50, 2003.

Wukitsch MW, Petterson MT, Tobler DR, and Pologe JA. Pulse oximetry: Analysis of theory, technology, and practice. *J Clin Monit* 4(4): 290–301, 1988.