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Is a Global Singular Hypertension Treatment Guideline that Would Improve Hypertension Control Achievable?

Gary L Murray[1]* and Joseph Colombo[2]

[1]Director of Medical Research, Heart and Vascular Institute, USA

[2]CTO and Senior Medical Director, Physio PS Inc., Atlanta GA, USA

Correspondence to: Gary L Murray, Director of Medical Research, Heart and Vascular Institute, USA; E-mail:drglmurray@hotmail.com

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Introduction

Approximately 1.5 billion people are hypertensive. We are sub-optimally dealing with this pandemic. Less than 50% of these patients are controlled, and both mortality and morbidity are increasing [1], despite our wide variety of pharmacologic therapies and a multitude of guidelines. A recent comparison of the AHA/AHACDC, ESH/ESC, ASH/ISH, and NICE guidelines all recommend 4 main drug classes: Angiotensin-Converting Enzyme Inhibitors [ACEI), Angiotensin Receptor Blockers (ARB), Calcium Channel Blockers (CCB), and Diuretics; with no need to emphasize differences between drugs within each class [2]. None recommend utilizing an assessment of the Sympathetic (S) and Parasympathetic (P) abnormalities we've identified over the past 14 years (frequently present) or using the results to identify which drug(s) to choose if S and P malfunction(s) are identified. Hypertension (HTN), by definition, is a hemodynamic disease, and there are major inter- and intra-class differences in the hemodynamic effects, which can be autonomically mediated, among the drugs we administer. One possible explanation for our difficulty controlling hypertension (HTN) is that we do not tailor therapy to each patient's pathophysiology. A blood pressure of 160/95 can be, with a few comorbid/cost exceptions or physician preferences, treated the same in every patient. Do we treat all cases of pneumonia, diabetes, or coronary diseases the same? In our defense, until recently, we couldn't do otherwise for HTN. But now we can more scientifically choose and adjust therapy; we have a tool that could assist in meeting this goal; a tool that's not being employed. So we continue treating the blood pressure per se.

The pathophysiology of Htn

Several causative mechanisms have been proposed [3,4]. Of these, we believe the neuro-adrenergic hypothesis [5-7] deserves the most attention since our autonomic testing of hypertensives has revealed autonomic (P&S) nervous system abnormalities prevalent in over 90% of patients. Increased S tone and Cardiac Output (CO) accompanied by low Systemic Vascular Resistance (R_s) typifies young hypertensives. Over the years, high S and CO decrease [8]. R_s increases, likely due to end-organ damage (Arterial Hypertrophy and Endothelial Dysfunction), uncoupling R_s from S, although S still influences it, as does P. The uncoupling causes decreased Baroreceptor Reflex (BR) and Cardiopulmonary Receptor sensitivity, accompanied by lowering of P activity [3,5-10]. If P<<S, Sympathovagal Balance (SB) is too high, which we have shown to increase Major Adverse Cardiovascular Events (MACE) 7-fold [11]. Obesity, alternatively, is associated with high S and HTN [12]. The complete relationship is: [Mean Arterial Blood Pressure (mBP)] – [mean right Atrial BP] = R_s x CO.

However, we only measure mBP (e.g., BP) while treating HTN. S & P profoundly affect both of the unmeasured variables in this equation, yet S & P are unmeasured as well. Incredibly, we don't measure major factors that alter the 2 unmeasured variables in the equation! So there are 4 values (S, P, R_s, CO), each of which differs in every patient, yielding a multitude of combinations affecting the BP we're attempting to control. No wonder we struggle.

A significant flaw in all current guidelines

By focusing on the BP per se without obtaining S & P measures initially, we assume the HTN to be primary,e.g., essential HTN, in at least 90% of hypertensives, with patients rarely having secondary HTN, such as Pheochromocytoma, Cushing's, etc. This is a false assumption, as HTN may be secondary, e.g., not essential, due to primary autonomic dysfunction such as Parasympathetic Excess (PE), Sympathetic Excess (SE, a beta-adrenergic response) (although common early in young essential hypertensives, SE isn't confined to them), and Sympathetic Withdrawal upon standing (SW, an alpha-adrenergic response). Treating HTN as primary, rather than secondary, when autonomic dysfunction (aka, Dysautonomia) is demonstrated results in poor outcomes. A full discussion of the effects of all of these Dysautonomias is beyond the scope of this article, so we'll focus on PE.

PE is perhaps the most pernicious of the Dysautonomias. PE is characterized as an abnormal Parasympathetic response to stress (exercise, upright posture, illness, injury, or emotional, psychological,

or physiological stresses, etc.), a Sympathetic challenge. Given that the Parasympathetic set the threshold around which the Sympathetic react, PE amplifies the Sympathetic response. This is why it is often "hidden" and only the SE is detected as abnormal BP, HR, or CO. PE can present as Anxiety, Chronic Regional Pain Syndrome, Addictions (since P is associated with brain stem pleasure/comfort centers), Chronic Fatigue, Sleep Disorders, Cognitive Disorder ("Brain Fog"), and difficult to control BP, blood sugar, or hormone level. The PE causes a secondary SE to preserve cerebral perfusion, resulting in secondary HTN. The pharmaceutical treatment of PE is 1/10th the traditional dose of anti-depressants (with normal to low SB) or very low dose carvedilol (with high SB or Cardiovascular Autonomic Neuropathy), not the current guidelines' recommended ACEI/ARB, CCB, or a diuretic (refer to Clinical Autonomic Dysfunction, by Colombo, et al.; Springer, 2014).

To improve HTN control, we must mathematically quantitate as many of these 4 factors as possible. Impedance Plethysmography had the potential for yielding BP, R_s, and CO, but it failed to provide us reliable information for HTN management. So we turned toward at least measuring S & P. Heart rate variability (HRV) = S + P. Until 2006, we could only measure HRV, forcing assumptions and approximations of the independent contributions of S & P to total HRV. Both S and P must be accurately identified (mathematically independently but simultaneously) to be clinically useful for managing HTN.

S & P testing for assistance choosing therapy

A technologic breakthrough (ANX 3.0 Autonomic Monitor, now the Physio PS 4.0 P&S Monitor) was developed, validated, and verified by the 1st joint Bio-Medical Engineering program group from Massachusetts Institute of Technology and Harvard [13-17], and is available for user-friendly routine clinical use. The independent contributions of S & P to HRV are quantified through 2 simultaneous measurements: ECG and Impedance Plethysmography. ECG monitoring establishes total HRV which is the sum of S + P. It is measured as the Low-Frequency area (LFa) which is under the HR time-frequency spectral curve between 0.04-0.15 Hz. LFa is a measure of total Autonomic activity (S + P). Impedance Plethysmography independently quantitates P. P is measured as the Respiratory Frequency area (RFa) which if the area under a (narrow) 0.12 Hz-wide window on the HRV spectral curve centered around the modal peak of the time-frequency Respiratory Activity (RA) spectral curve. In this way, P accurately follows RA, for example, in modeling Respiratory Sinus Arrhythmia responses of the Parasympathetic nervous system. P is no longer assumed to be the fixed, wide-band, an area under the HRV curve between 0.15-0.40 Hz. Since HRV due to RA is solely P-dependent, S is now quantified as HRV – P. Since P can fall into the 0.04-0.15 Hz window which is the low-frequency region of the HRV spectral curve typically assumed to represent S-activity, LFa = HRV - P accounts for this and prevents a misinterpretation of S. The time-frequency HRV and RA curves are analyzed using continuous wavelet transforms rather than the previously employed frequency-only fast Fourier transforms that compromise time and frequency resolution due to its use of fixed-length windows in the analysis.

All current HTN guidelines recommend 4 main drug classes (Angiotensin-Converting Enzyme Inhibitors [ACEI], Angiotensin Receptor Blockers [ARB], Calcium Channel Blockers [CCB], and Diuretics) without attempting to match their S & P effects to each patient's autonomic profile. This can result in choosing therapies doomed for failure since the goal is lowering BP per se independent of the specific therapy's S & P effects. This method of treatment often mismatches the therapy to the patient's autonomic measures, resulting in a poor initial response or activation of compensatory mechanisms, resulting in recidivism (about 25% of patients [18] that combat, for example, Sympathetic Withdrawal (SW) or Parasympathetic Excess (PE) upon standing upright, both indicative of BR dysfunction, orthostatic dysfunction, or drug effect.

We performed a feasibility study comparing S & P assisted HTN therapy to JNC 8 therapy [19]. Forty-six patients were randomized. Of the S & P assisted Group 74% achieved JNC goals vs. 30.4% of the JNC 8 treated Group ($p<0.001$, home and office systolic and diastolic BP). The office P & S mean measures are listed in (Table 1).

Final S was lower sitting and P was higher sitting and standing ($p<0.001$) in the S & P Group. These results required 2.3 prescription drugs in the S & P Group *vs.* 3 in the JNC 8 Group. (Tables 2, 3, and 4) are individual patient examples.

Table 1: P&S Mean Measures.

	P&S Guided Therapy		JNC8-Guided Therapy		
	Initial	**Final**	**Initial**	**Final**	**p**
Resting pulse	82	61	76	72	<0.001
LFa (bpm2)	2.11	0.9	0.57	1.19	<0.001
RFa (bpm2)	2.15	0.71	0.47	0.62	<0.001
sBP (mmHg)	151	138	155	146	<0.001
dBP (mmHg)	74	71	73	65	<0.001
SB* (unitless)	3.26	1.86	1.83	1.84	0.004
Standing					
LFa (bpm2)	3.19	2.35	0.67	2.31	ns
RFa (bpm2)	1.67	1.56	0.5	0.875	0.005
sBP (mmHg)	153	138	155	145	<0.001
dBP (mmHg)	79	71	73	65	<0.001

dBP=diastolic blood pressure; LFa=low frequency area (S); P=parasympathetic; RFa=respiratory frequency area (P); SB=Sympathovagal Balance; sBP=systolic BP.

Table 2: (Recidivism) 80 y/o Group 2 patient with recidivism due to PE standing. Medications: (A) 100 mg. Metoprolol and 100 mg Losartan/d; (B), (C): Metoprolol and Losartan were changed to Telmisartan 40/5/12.5 mg and Bystolic 20 mg/d. Bystolic increases standing P-tone (RFa) (long-term administration of Metoprolol would have lowered it) (C) resulting in a compensatory increase in S-tone (LFa) to maintain BP; Amlodipine also increases S-tone. Bystolic should be switched back to Metoprolol or to Clonidine, low dose TC or SSRI could be added, Amlodipine discontinued and (r)-ALA added.

Sitting	**(A)**	**(B)**	**(C)**
LFa (bpm2)	0.18	0.2	0.38
RFa (bpm2)	0.14	0.18	0.07
SB	1.3	1.12	5.41
BP (mmHg)	175/68	149/59	193/79
Standing			
LFa (bpm2)	0.46	0.82	4.1
RFa (bpm2)	0.69	0.28	5.96
BP (mmHg)	176/76	139/66	179/68

Table 3: 76 y/o Group 1 patient with uncontrolled HTN taking Coreg 12.5 mg bid, 10 mg Ramipril 10 mg/d (A) Standing high RFa (PE) with secondary high LFa are present, as is high SB. (r)-ALA was added (B), associated with improvement of theses abnormalities (Same as Table 2).

Sitting	**(A)**	**(B)**
LFa (bpm2)	0.30	0.40
RFa (bpm2)	1.22	0.36
SB	2.7	1.08
BP (mmHg)	166/65	136/56
Standing		
LFa (bpm2)	22.32	0.15
RFa (bpm2)	3.50	0.41
BP (mmHg)	172/67	147/65

Table 4: 76 y/o Group 1 patients with SW on Losartan 100 mg/d and Amlodipine 10 mg/d (A). Medications were changed to Clonidine 0.1 mg bid and (r)-ALA, correcting SW (B) (Same as Table 2).

Sitting	(A)	(B)
LFa (bpm2)	0.09	0.01
RFa (bpm2)	0.18	0.03
SB	0.5	0.25
BP (mmHg)	190/86	151/65
Standing		
LFa (bpm2)	0.02	0.02
RFa (bpm2)	0.04	0.02
BP (mmHg)	165/86	150/60

To use S & P measures to guide therapy, one must know the S & P effects of anti-hypertensives for the individual patient. For example, in general, Amlodipine increases SB, while beta-blockers decrease it; only Carvedilol among beta-blockers and ACEI/ARBs improve BR sensitivity (BRS), while non-Dihydropyridine CCBs decrease it [20-23]. However, sympatholytic such as these worsen standing SW (except for Clonidine due to its central mechanisms of action and increased BRS [21,25]. More SW, for example, causes patients to become more lightheaded (increases orthostatic dysfunction) leading to non-compliance. In cases of HTN secondary to PE, the central alpha action of Carvedilol, low dose SSRIs and Tricyclics (TC) lower PE which will relieve secondary SE which will lower BP and eventually relieve (secondary) HTN organically, assuming no end-organ effects. Once, the P&S nervous systems are balanced for the individual patient, any remaining high BP or HTN may be treated as primary HTN with a more stable patient.

We utilized S & P measures to choose anti-hypertensive therapy as follows: 1) If S & P balance (resting SB) was normal, any therapy was chosen; 2) if SB was high due to a relative or absolute SE, a sympatholytic was given; 3) If SB was high due to low P, an ACEI/ARB and/or Diltiazem was given; (r) Alpha lipoic acid (rALA) can raise low P, so rALA was used as well. Upon standing, if no SW, any anti-hypertensive was chosen. If SW was noted, sympatholytics were avoided (excepting Clonidine or Carvedilol) as were Diltiazem and diuretics; Amlodipine, Hydralazine and/or rALA (which can raise S) were used. If PE occurred upon standing, diuretics and sympatholytics were avoided, except low dose Carvedilol. For PE upon standing, low dose SSRI or very low-dose TC were preferentially prescribed.

Diuretics were used for dependent edema only, since they don't improve endothelial dysfunction; unlike rALA, ACEI/ARB, CCB, and 3rd generation beta blockers [26-29].

Conclusion

Hypertension is an enormously prevalent, life-threatening condition with a high morbidity that consumes tremendous health-care expenses. I'm shocked that we've had to treat it with no specific testing for guidance. Choosing the wrong treatment, while initially lowering BP, will trigger compensatory measures often involving S and P changes [30-34] necessitating periodic re-evaluation of S and P that "fight" the therapy, resulting in higher doses of more medications, increased treatment side-effects, frustration, resistant HTN, and a reduced quality of life.

The ANX 3.0 Autonomic Monitor (now Physio PS 4.0 Monitor) is a harmless, inexpensive, 15-20 minutes test that may prove to be tremendously helpful for treating HTN. It deserves a rigorous evaluation to establish its role in HTN management. In my practice, it's invaluable and serves as my guideline. Approximately 75% of my patients' HTN is controlled, without recidivism or masked, uncontrolled HTN (MUCH).

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