Pulsatile hemodynamics of hypertension: systematic review of aortic input impedance

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Objective: Input impedance is the frequency-dependent afterload to pulsatile blood flow. Studies of input impedance have been performed as early as the 1960s and have been applied to hypertension (HTN). However, to date, these studies have not been systematically evaluated. This systematic review aims to summarize the literature, interpret existing data from the perspective of impedance theory, and to discuss their potential for generating physiological insights into HTN.

Methods: We identified 11 studies wherein computed impedance moduli from both HTN and control (CNT) groups were reported. In addition, we performed bivariate analyses of raw data from three of these studies.

Results: Major findings include HTN groups had consistently elevated impedance moduli at 0 Hz (Z_0) and at heart rate frequency (Z_1), an increased frequency wherein impedance phase first crosses 0 (f_0), but no consistent pattern in characteristic impedance (Z_c), when compared to CNT groups; SBP and DBP are highly correlated with Z_0 and Z_1, moderately correlated with f_0, less correlated with Z_c; the measurement and calculation methods for Z_c are varied and inconsistent; and a not insignificant proportion of hypertensive individuals have 'normal' Z_0, Z_1 and Z_c values. These findings are limited by the heterogeneous study populations and small sample sizes.

Conclusion: These findings suggest that Z_0, Z_1 and f_0 are significantly associated with HTN, whereas the role of Z_c is less clear. Additional studies are needed to evaluate these input impedance variables in order to generate substantial implications in clinic settings.

Keywords: characteristic impedance, hypertension, input impedance, wave reflection

Abbreviations: CNT, control; f_0, the frequency where input impedance phase first crosses zero; HR, heart rate; HTN, hypertension; MBP, mean blood pressure; PP, pulse pressure; ROC, receiver operating characteristic; Z_0, input impedance modulus at 0 Hz; Z_1, input impedance modulus at the first harmonic; Z_c, characteristic impedance

INTRODUCTION

Despite the availability of multiple antihypertensive medications, surveys show that only half the patients with hypertension (HTN) are able to adequately control their blood pressure [1]. Although factors such as noncompliance, drug side effects and poor access to healthcare are important contributors, our limited understanding of the dynamic and spectral features of HTN may also play a role. Input impedance describes the frequency-dependent opposition to blood flow and provides a more complex assessment of blood flow/pressure than peripheral resistance alone. By evaluating impedance across multiple frequencies, input impedance can capture underlying physiological processes – such as wave reflections and aortic (visco)elasticity – that may be important determinants for systemic blood pressure. Input impedance was suggested by McDonald and Taylor [2] as early as in 1959, implemented by O'Rourke [3] and explained in detail in text books of *Hemodynamics* by Milnor [4] and *MacDonald's blood flow in arteries* by Nichols and O'Rourke [5].

In general, the input impedance of the ascending aorta possesses the following characteristics: the modulus (or amplitude) of the input impedance is greatest at zero frequency; with increasing frequency, the modulus decreases in magnitude toward a minimal value, which is commonly located between the second and fourth harmonics [i.e. frequencies corresponding to two to four times the heart rate (HR)] and is approximately 5–10% of the input resistance (zero frequency impedance); the input impedance moduli settle and fluctuate around a steady-positive impedance value (Z_c, the characteristic impedance).

Past physiological studies have predominantly focused on two aspects of the aortic input impedance: Z_0 and Z_c. Z_0 is the peripheral vascular resistance and embodies impedance to flow as if the flow were steady and continuous. Z_c, on the contrary, is the impedance at higher frequencies and is generally attributed to the local aortic wall stiffness and diameter. Other reported impedance parameters include f_0 – the frequency wherein input impedance reaches its first minimum and its phase first crosses zero – and Z_1, the impedance modulus at the heart-rate frequency [6]. f_0

Journal of Hypertension 2012, 30:1493–1499

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Received 12 January 2012 **Revised** 22 March 2012 **Accepted** 17 April 2012

DOI:10.1097/HJH.0b013e328354e81d

reveals information about wave reflections, with a higher f_0 indicating earlier reflections.

Studies of aortic input impedance have been specifically applied to HTN populations. However, to date, these studies have not been systematically evaluated. This review aims to summarize the existing evidence, to interpret the data from the perspective of impedance theory and to discuss their potential for generating physiological insights into HTN.

METHOD

This systematic review includes 11 articles [7–17] from two electronic databases: *PubMed* and *Scientific Citation Index* for dates ranging from the database inception to May 2010. The searching keywords were 'impedance', 'input resistance' and 'windkessel model' crossed with the keywords 'HTN ', 'high blood pressure' and 'hypertensive'. Searches were limited to the English language. We also manually searched the references of all relevant publications. Articles were selected if the studies contained in-vivo human data; had primary-collected data and were not review articles, commentaries or editorials; involved both control (CNT) normotensive individuals and systemic hypertensive individuals and had central input impedance measured/calculated. Exclusion criteria were that the studies had patients with effects of pharmacological drugs (we required the hypertensive patients were either never treated or withdrawn from the drug for at least a week) and had patients with other severe cardiovascular comorbidities.

Extracted data includes participants, age, HR, SBP, DBP, Z_0, Z_1, Z_c and f_0. Other parameters such as input impedance phase, cardiac output, stroke volume and total/mean work power were evaluated but ultimately excluded due to limited data availability from the articles for comparison. In cases in which different units were employed, appropriate unit conversions were performed.

In a number of studies, the published raw data were employed for bivariate analysis. Primary authors of selected studies were also contacted to obtain additional raw data but with no success. Scatter plot matrix was computed from JMP (SAS Corporate, Cary, North Carolina, USA) with Pearson correlation method and density ellipse was displayed with 95% as the confidential interval. Greater narrowing of the ellipse along the diagonal axis indicated greater correlations (coefficient $r > 0.5$), whereas rounding of the ellipse and absence of a diagonal orientation suggested lack of correlation ($r < 0.5$) between variables.

We also determined the receiver operating characteristic (ROC) curve with the raw data for Z_0, Z_1, Z_c and f_0 in regards to the diagnosis of HTN.

RESULTS

Table 1 summarizes the data extracted from the selected studies. Patients' characteristics including sex and age are listed and categorized according to the group designations (CNT vs. HTN) if the information was provided. In addition, the type of HTN (essential/permanent vs. isolated systolic vs. mixed HTN) is also listed. Overall, seven out of 11 studies [7–13] evaluated essential HTN, whereas two studies assessed isolated systolic [15,16], one investigated mixed HTN [17] and one study did not indicate the type of HTN [14]. With the exception of studies by Ferrier *et al.* [16] and Mitchell *et al.* [17], study participants were predominantly men. Study by Mitchell *et al.* [17] performed separate

TABLE 1. Extracted data from the 11 selected articles

Study	Participants	Age	HR (beat/min)	SBP (mmHg)	DBP (mmHg)	Z_0	Z_1	Z_c	f_0
Merillon *et al.* [7]	CNTL (11 M, 2 F)	**40**	79	**109.8**	**73.7**	**1140**		90	**4.3**
	Essential HTN (12 M)	**51**	83	**174.4**	**100.8**	**1680**		114	**5.2**
Merillon *et al.* [8]	CNTL (10 M, 1 F)	**38**	81	**112**	**73**	**1173**		100	
	Permanent essential HTN (11 M)	**50**	84	**171**	**100**	**1677**		104	
Merillon *et al.* [9]	CNTL (25 M)	43	**75**	**119**	**72**	**1270**		**101**	
	Essential HTN (19 M 1 F)	47	**85**	**171**	**101**	**1712**		**134**	
Ting *et al.* [10]	CNTL (7 M 1 F)	41.9	97.2	**120.2**	**74.8**	**1713.3**	**165.1**	**93.9**	**2.97**
	Essential HT (6 M 5 F)	34.8	79.2	**158.6**	**92.5**	**2294.9**	**300.7**	**145.7**	**4.15**
Ting *et al.* [11]	CNTL (7 M 3 F)	34.5	87.4	**115.7**	**77.3**	**1268**	**105**	77.9	**3.5**
	Essential HTN (8 M 4 F)	33.8	86.8	**162.4**	**102.5**	**1962**	**200**	82.5	**4.6**
Ting *et al.* [12]	CNTL (10 M 4 F)	32.6	83.5	**111.8**	**73.5**	**1239**	**110**	**75.5**	
	Essential HTN (9 M 3 F)	37	79.7	**156.9**	**96.2**	**1612**	**185**	**60.4**	
Ting *et al.* [13]	(CNT is same as Ting CT 1993)	32.6	83.5	**111.8**	**73.5**	**1239**	**110**	75.5	**3.1**
	Essential HTN (8 M 4 F)	32.9	82.3	**160.6**	**100.2**	**1863**	**220**	71.9	**4.3**
Chang *et al.* [14]	CNTL (5 M 2 F)	46	75	**122**	**74**	**1651**	**177**	**122**	**3.4**
	HTN (7 M 2 F)	49	79	**180**	**100**	**2751**	**383**	**193**	**4.8**
Nichols *et al.* [15]	CNTL (9)	58	78	**134**	80	**1395**	**210**	**89**	
	Isolated systolic HTN (9)	58	76	**166**	84	**2013**	**329**	**184**	
Ferrier *et al.* [16]	CNTL (10 M 10 F)	64	62	**119**	<90		**191.2**	**133.6**	
	Isolated systolic HTN(10 M 10 F)	64	64	**154**	<90		**261.6**	**187.2**	
Mitchell *et al.* [17]	CNTL (11 F)	56	68	**114**	**64**	**1686**	**236**	**185**	
	Mixed HTN (50 F)	61	65	**167**	**83**	**2415**	**444**	**268**	
	CNTL (19 M)	60	62	**125**	**69**	**1673**	**221**	**159**	
	Mixed HTN (78 M)	60	63	**162**	**88**	**2131**	**314**	**208**	

F, female; HR, heart rate; M, male; Z_0, input impedance at 0 Hz (dyn s/cm^5); Z_1, first modulus of input impedance (dyn s/cm^5); Z_c, characteristic impedance (dyn s/cm^5); f_0, frequency wherein input impedance reaches its first minimum and its phase first crosses zero.

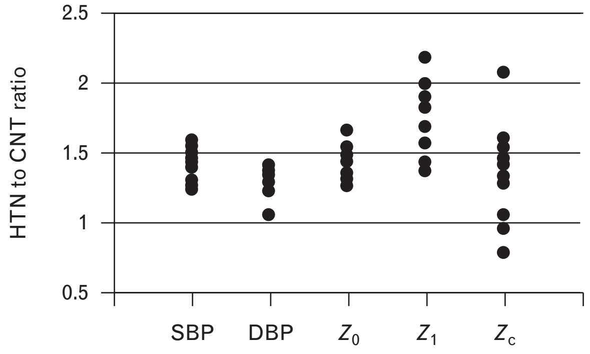

FIGURE 1 Plot of the variable ratios between hypertension (HTN) and control (CNT) groups. Variables include SBP, DBP, input impedance at 0 Hz (Z_0), first modulus of input impedance (Z_1) and characteristic impedance (Z_c).

analyses according to sex. The HTN individuals within the isolated systolic and mixed HTN studies were generally older, although two essential HTN studies by Merillon *et al.* [7,8] had older hypertensive groups yet statistically younger CNT groups (bold fonts indicate statistically significant differences between HTN and CNT groups).

Table 1 also lists the mean values for the HR, blood pressure and input impedance parameters for each of the studies. Across all studies, Z_0 and Z_1 are significantly increased in the HTN group compared with the CNT group. Z_c, however, did not display the same consistency and five of the 11 studies showed either no significant difference between the two groups or reduced Z_c values in the HTN group. The three studies [15–17] involving isolated and mixed HTN and with older participants, however, were consistent with relative increases in Z_c for HTN patients.

The magnitudes of Z_0 are six to 12-folds greater than that of Z_1, whereas Z_c amplitudes are generally smaller than that of Z_1. For the five studies reporting zero crossing frequencies, the mean f_0 was uniformly increased in HTN group as compared to the CNT group.

Figure 1 illustrates the aggregated results in graphical form. The HTN to CNT ratios of mean Z_0 magnitudes were generally 1.5 across studies and were comparable to the ratios of mean SBP and partially to the ratios of mean DBP. The HTN to CNT ratio for Z_1 revealed a much greater range of ratios from 1.4 to 2.2. As noted previously, the ratios of Z_c were not consistent across studies, and although mean Z_c magnitudes were generally increased in hypertensive patients, some studies – notably study by Ting *et al.* [12] – demonstrated reduced Z_c.

Table 2 lists the devices and methods used to acquire blood pressure and flow measurements. In addition, the mathematical methods for calculating Z_0 and Z_c are also summarized. Most studies used intravascular catheter measurements, whereas Ferrier *et al.* and Mitchell *et al.* employed applanation tonometry at the carotid artery and Doppler imaging of the left ventricle outflow tract. Across the selected studies, four different methods were used to calculate Z_c: the average modulus of input impedance above 4 Hz [7,8,10–13]; averaged input impedance above 2 Hz [14–16]; indirect derivation of Z_c from pulse wave velocity using the Waterhammer formula $Z_c = \frac{\rho C}{\pi r^2}$ (where ρ is the density of blood, C is the wave velocity, r is the diastolic aortic radius) [9] and a time-domain approach wherein characteristic impedance was calculated as $\Delta P/\Delta Q$ in early systole [17]. The methods for obtaining Z_1 were not included in Table 2 because Z_1 was derived as the ratio of first blood pressure harmonic modulus to first blood flow harmonic modulus in the seven studies wherein this information was detailed. No detailed description was provided in study by Mitchell *et al.*

To further explore the detailed relationships between input impedance and blood pressure parameters [SBP,

TABLE 2. Locations and methods of the measurement of blood pressure and flow, and the method in the calculation of input impedance at 0 Hz and characteristic impedance

Paper	Measurement	Device	Z_0 calculation method	Z_c calculation method
Merillon *et al.* [7]	Ascending aorta pressure and blood flow	Catheters with micromanometer and flowmeter sensor	P_0/Q_0 (P_0: pressure harmonic modulus at 0 Hz, Q_0: flow harmonic modulus at 0 Hz)	Averaging of all moduli of input impedance above 4 Hz
Merillon *et al.* [8]	Same as Merillon *et al.* [7]	Same as in Merillon *et al.* [7]	Same as Merillon *et al.* [7]	Same as in Merillon *et al.* [7]
Merillon *et al.* [9]	Left ventricular and aortic pressure	Mcromanometer mounted on catheter	$80 \times P/CO$ (P: mean aortic pressure, CO: cardiac output)	$\rho C/\pi r^2$ (r: diastolic aortic radius, C: pulse wave velocity, ρ: density of blood
Ting *et al.* [10]	Left ventricular and ascending aortic pressure and aortic flow velocity	Catheter with pressure and velocity sensors	$(P_v - P_a)/Q$ (P_v: average ventricular pressure; P_a: average atrial pressure; Q: mean blood flow)	Same as in Merillon *et al.* [7]
Ting *et al.* [11]	Same as Ting *et al.* [10]	Same as Ting *et al.* [10]	Same as Ting *et al.* [10]	Same as in Merillon *et al.* [7]
Ting *et al.* [12]	Same as Ting *et al.* [10]	Same as Ting *et al.* [10]	Same as Ting *et al.* [10]	Same as in Merillon *et al.* [7]
Ting *et al.* [13]	Same as Ting *et al.* [10]	Same as Ting *et al.* [10]	Same as Ting *et al.* [10]	Same as in Merillon *et al.* [7]
Chang *et al.* [14]	Ascending aorta flow velocity and pressure	Multisensor catheter	Quotient of mean aortic pressure and cardiac output	Averaging of all moduli of input impedance above 2 Hz
Nichols *et al.* [15]	Ascending aortic blood flow velocity and aortic and left ventricular pressure	Catheter mounted with multisensors	P/Q (P: mean pressure, Q: mean flow)	Averaging of all moduli of input impedance above 2 Hz
Ferrier *et al.* [16]	Carotid artery pressure, volumetric aortic flow	Applanation tonometry and handheld doppler velocimeter	Cardiac output derived from velocity flow was used to calculate total peripheral resistance	Averaging of all moduli of input impedance above 2 Hz
Mitchell *et al.* [17]	Carotid artery pressure and left ventricular outflow tract flow	Tonometry and pulsed doppler	Peripheral resistance (no method was mentioned)	$\Delta P/\Delta Q$ (ΔP and ΔQ: pressure and flow difference in the early systolic period)

Z_0, input impedance at 0 Hz; Z_c, characteristic impedance.

DBP, mean BP (MBP), and pulse pressure (PP)], the primary data from three of these 11 articles [7,10,14] were concatenated (article by Merillon *et al.* [7] lacked Z_1 data) and are listed in Table 3. We also compared age distributions in the CNT (41.82 ± 10.68) and HTN groups (44.97 ± 12.68), which are not significantly different. The bivariate relationships are plotted in Fig. 2. The figure shows scatter plots with coefficient correlations and an overlying density ellipse with 95% as the confidential interval. There are strong correlations ($r > 0.5$) between Z_0 and SBP, MBP, PP and between Z_1 and SBP, MBP, PP. Weak correlations exist between Z_c and SBP, DBP, MBP, PP. The correlation between f_0 and blood pressure parameters are weak but otherwise strongest between f_0 and Z_1.

The scatter plots in the figure also have group designation markers: '-' for CNT and 'o' for HTN. A clear distinction is noted between CNT and HTN individuals with respect to SBP, DBP and MBP, as these parameters were used as inclusion/exclusion criteria. However, the differences in PP values between the two groups are less distinct and even much less so for the input impedance parameters Z_0, Z_1, Z_c and f_0. For these latter variables, substantial overlap between the two groups exists, particularly for Z_c. A not insignificant proportion of hypertensive individuals have 'normal' input impedance parameters (based on the ranges of values for the normal individuals). Conversely, some normal individuals have elevated input impedance values, although such cases are comparatively less common.

With this subset of participants, the area under ROC curves for Z_0, Z_1, Z_c and f_0 in regards to the diagnosis of HTN were 0.80, 0.88, 0.72 and 0.80, respectively.

DISCUSSION

This systematic review identified 11 studies that reported input impedance data for both normotensive (total $N = 147$) and hypertensive patients ($N = 256$). Collectively, the existing evidence suggests that based on mean input impedance and blood pressure values, HTN groups had consistently elevated Z_0, Z_1 and f_0 values compared to the CNT groups but no consistent pattern with Z_c amplitudes; based on individual, raw data analysis of three studies, SBP and DBP are highly correlated with input impedance parameters Z_0 and Z_1, somewhat correlated with f_0, but less correlated with Z_c; the measurement and calculation methods for Z_c are varied and inconsistent and a not insignificant proportion of hypertensive individuals have 'normal' Z_0, Z_1 and Z_c values. From a physiological standpoint, these data imply that peripheral vascular resistance (Z_0), input impedance at the heart beat frequency (Z_1), and wave reflection (f_0) are important factors associated with HTN, whereas the role of aortic stiffness and aortic diameter (Z_c) is less clear in these hypertensive individuals.

The significant correlation between peripheral vascular resistance (Z_0) and HTN is not a new finding and consistent with the understanding that vasoconstriction (possibly from enhanced sympathetic nervous activity) plays a prominent role in HTN pathophysiology. Whether this vasoconstriction plays a causative and pathogenic role or is an abnormal response to persistently elevated blood pressure remains unclear [18,19].

In our raw data analyses, Z_1 demonstrated the strongest correlation with SBP and PP than any other reported input impedance parameter. Moreover, Z_1 was associated with greatest area under the ROC curve for the diagnosis of HTN compared to Z_0, Z_c and f_0. However, the total number of studies evaluating Z_1 in HTN remains low, and the physiological implication of Z_1 is itself ambiguous. Based on the bivariate data, Z_1 also has the unique feature of being highly correlated with all other input impedance parameters reported here: Z_0 (peripheral resistance), Z_c (aortic stiffness and diameter) and f_0 (wave reflection). From a mechanistic standpoint, this may be observed because the frequency is low enough to be influenced by peripheral resistance and possibly high enough to be influenced by aortic stiffness. Additionally, Z_1 resides in the time domain wherein wave reflections have taken effect [first harmonic frequency (approximately 1 Hz) <minimum modulus frequency (approximately 2–4 Hz)]. As a consequence, Z_1 may reflect the composite properties that personify the vascular system and, thereby, be a useful global marker for the impedance confronting the pulsating heart, particularly for HTN. Naturally, additional studies should be performed before a definitive conclusion can be made.

The zero-crossing frequency (f_0) was significantly increased in hypertensive patients compared to normotensive CNTs in all five studies reporting this information. Furthermore, by the bivariate data, a moderate positive correlation ($r > 0.4$) between f_0 and SBP is seen. An increased f_0 occurs when either the pressure/flow wave velocity increases or the effective distance to reflection sites are decreased. According to past studies, the former scenario is more likely and can be explained by the aortic distention resulting from elevated pressures and the accompanying increase in elastance (stiffness), which subsequently increases pulse wave velocities [20]. This early reflection generates a temporal (earlier) shift in the retrograde wave at the ascending aorta to coincide with the outgoing systolic pressure wave, thus explaining for the moderate correlation between SBP and f_0.

According to the raw data, f_0 is not correlated with either Z_0 or Z_c. From a theoretical standpoint, f_0 and Z_c are expected to be correlated because earlier reflections (as indicated by increased f_0) result from an increase in aortic stiffness (which greatly determines Z_c). However, Z_c is also inversely related to the aortic radius to the power of 2.5, and the increase in radius accompanying HTN may effectively nullify any increase in Z_c attributed to enhanced wall stiffness. As a consequence, wave reflection (f_0) appears to be an important, separable variable with respect to systolic HTN.

As already made evident, characteristic impedance is a complicated variable influenced by not only arterial stiffness but also vessel radius. Its inverse relationship with aorta radius may partially explain for the inconsistencies in HTN to CNT ratios of Z_c seen across the selected studies and also for the relatively weak correlation between Z_c and blood pressure parameters in the aggregated raw data. This confounding factor has been mentioned by researchers before [21]. In addition, the data suggests an age effect as

TABLE 3. Raw data from three of the 11 reviewed studies

paper	Participants	Age	SBP	DBP	MBP	PP	Z_0	Z_1	Z_c	f_0
Merillon JP *et al.* [7]	N1	47	96.8	65.3	79.5	31.5	840		42	3.1
	N2	30	100.5	65.3	82.5	35.3	1140		90	3.9
	N3	22	106.5	69.0	87.8	37.5	1140		108	3.4
	N4	45	87.8	62.3	76.5	25.5	1260		126	3.6
	N5	41	126.0	81.8	102.0	44.3	1080		78	4.7
	N6	26	94.5	65.3	81.0	29.3	960		54	3.8
	N7	58	117.8	75.8	93.8	42.0	1200		60	5.8
	N8	25	114.0	84.8	100.5	29.3	1080		120	4.0
	N9	53	108.0	69.0	84.0	39.0	780		72	3.3
	N10	32	121.5	87.0	102.8	34.5	1260		72	5.7
	N11	56	120.8	78.8	97.5	42.0	1260		150	4.6
	N12	56	117.8	76.5	94.5	41.3	900		60	5.7
	N13	30	114.0	79.5	102.8	34.5	1620		138	3.7
Ting CT *et al.* [10]	N1	30	126.9	76.0	100.7	50.9	2288	272	238	3.51
	N2	56	139.6	73.0	100.7	66.6	1741	234	68	1.96
	N3	37	106.1	72.2	88.2	33.9	1393	108	138	2.49
	N4	39	126.9	102.9	114.3	24.0	935	41	44	3.07
	N5	40	113.0	69.0	90.3	44.0	2168	243	147	2.89
	N6	37	115.2	75.4	93.9	39.8	1434	118	95	3.10
	N7	45	113.5	80.5	97.2	33.0	1794	121	56	2.92
	N8	51	125.9	77.5	100.6	48.4	1855	181	113	3.30
Chang *et al.* [14]	N1	56	137	82	108	55	1994	234	147	3.9
	N2	37	118	79	98	39	1182	101	98	2.9
	N3	45	122	64	89	58	1358	204	116	4.1
	N4	40	111	66	88	45	1979	232	162	3.4
	N5	55	130	77	103	53	1824	238	119	2.5
	N6	36	111	67	89	44	1274	156	123	4.1
	N7	46	124	82	101	42	1949	74	87	2.7
Merillon *et al.* [7]	H1	44	165.8	85.5	118.5	80.3	1260		60	6.1
	H2	58	176.3	105.8	139.5	70.5	1800		222	5.5
	H3	59	204.8	94.5	133.5	110.3	1680		42	4.4
	H4	53	243.8	117.0	164.3	126.8	2520		36	4.6
	H5	59	152.3	94.5	120.0	57.8	1680		48	5.1
	H6	52	162.8	96.8	126.0	66.0	1260		60	6.1
	H7	29	136.5	96.0	114.8	40.5	1440		102	4.9
	H8	51	170.3	111.8	135.0	58.5	1800		96	4.6
	H9	59	164.3	82.5	117.8	81.8	1680		126	5.7
	H10	36	192.8	112.5	144.8	80.3	1920		204	5.5
	H11	60	156.8	103.5	127.5	53.3	1320		162	4.7
	H12	52	163.5	103.5	129.8	60.0	1920		240	5.2
Ting *et al.* [10]	H1	30	165.7	98.0	128.3	67.7	1379	160	113	4.05
	H2	25	142.8	93.6	118.8	49.2	2068	195	121	4.89
	H3	35	211.6	123.0	159.8	88.6	2721	377	154	4.41
	H4	34	151.8	92.3	122.1	59.5	1481	165	126	2.26
	H5	35	153.4	87.1	118.2	66.3	2968	425	173	3.98
	H6	44	160.8	90.9	121.6	69.9	4768	656	361	3.47
	H7	53	161.9	90.4	119.7	71.5	2127	278	145	3.86
	H8	46	167.1	92.1	123.2	75.0	2327	362	185	3.69
	H9	30	206.6	128.0	162.1	78.6	2774	349	169	4.11
	H10	25	172.3	95.3	129.7	77.0	3175	518	148	5.20
	H11	26	148.5	93.5	121.1	55.0	1797	199	128	4.53
Chang *et al.* [14]	H1	31	151	90	120	61	3174	412	131	5.7
	H2	33	151	100	126	51	1942	219	154	4.4
	H3	58	176	88	125	88	2164	396	288	3.5
	H4	62	163	72	108	91	2567	516	279	4.9
	H5	65	203	100	146	103	3875	518	197	6.6
	H6	40	222	132	173	90	3817	459	157	5.4
	H7	56	177	90	125	87	2454	428	216	4.4
	H8	56	208	115	154	93	2424	299	218	4.5
	H9	43	165	117	137	48	2344	203	99	4.2

Mean blood pressure (MBP) and pulse pressure (PP) were calculated from SBP and DBP as $\mathrm{MBP} = \mathrm{SBP}/3 + 2 \times \mathrm{DBP}/3$, $\mathrm{PP} = \mathrm{SBP} - \mathrm{DBP}$.

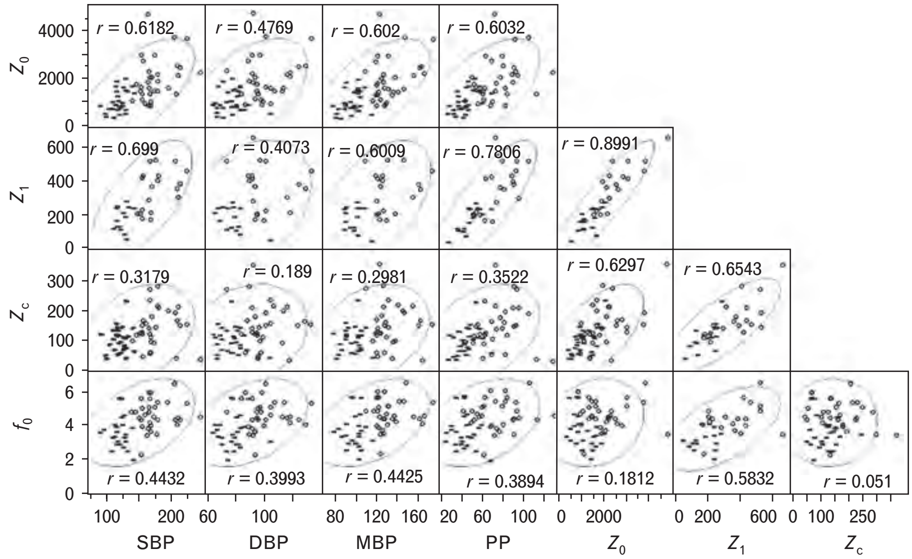

FIGURE 2 Scatter plots of the raw data with group designation markers. -, denotes the control individuals; o, is for the hypertensive patients. The figure also showed the density ellipses depicting the 95% of the confidential interval.

well. The younger HTN cohort for three studies by Ting *et al.* had reduced Z_c, whereas the older HTN groups in studies by Ferrier *et al.*, Mitchell *et al.* and Nichols *et al.* had significantly increased characteristic impedances compared to their respective CNT groups.

The inconsistencies in Z_c ratios across studies may also stem from the variable methods used to derive Z_c. As documented in Table 2, four different approaches were used to calculate Z_c. Two relied on the frequency-domain approach, albeit with different frequency cutoffs; one invoked a time-domain approach; and one calculated Z_c indirectly by using the Water–Hammer formula. Although the technical strengths and limitations for each approach are beyond the scope of this review, a more transparent and consistent approach is needed if Z_c is to be broadly applied to the clinical setting as some have advocated [22]. The need for consistency becomes more poignant in light of past studies showing how different characteristic impedance values can be obtained from the same data [3]. Moreover, HTN may be particularly susceptible to variabilities in Z_c if Z_c is derived in the frequency domain. Due to the increased zero-crossing frequency, a frequency-domain cutoff of 2 Hz, for instance, will likely incorporate the impedance minimum and, thus, potentially distort the final characteristic impedance results (which should theoretically be without any reflection effects).

The raw bivariate data evaluated in this review were useful in identifying the overlap in input impedance variables between the HTN and CNT groups. The overlap did not occur due to increased incidences of elevated input impedance variables (particularly Z_0 and Z_1) in CNT individuals. Rather, there were more incidences of HTN individuals having 'normal' ranges of input impedance values. Given the limited number of individuals within this raw data sample and the variable analytical methods, this observation will have to be confirmed with additional studies but, if true, will carry substantial implications for the clinician taking care of a hypertensive patient. The elevated pressure may originate from a specific physiological cause (e.g., elevated peripheral vascular resistance vs. aortic stiffness vs. wave reflection effects), and a dynamic approach such as aortic input impedance may help clinicians determine which specific cause is involved and subsequently what medication should be prescribed.

This review has identified some suggestive relationships between input impedance and blood pressure parameters, but the existing evidence for aortic input impedance in HTN is still inadequate. Only 11 studies were identified in this review and the number of individuals per study was generally small (with the exception of study by Mitchell *et al.* [17]). These studies did not report data on body size (i.e. height, weight), a known contributing factor to impedance measurement [23]. In addition, the analyzed raw data were a composite of only three studies. The level of evidence is insufficient to conclude how input impedance may differ between the types of HTN (i.e. isolated HTN vs. essential HTN), much less understand the effects of age and sex. Importantly, the majority of the studies involved younger participants with essential HTN who generally possess different pathophysiologies than older individuals with isolated systolic HTN. Aside from the aforementioned need for consistent Z_c derivation methods, the methods for acquiring pressure and flow data needed for aortic input impedance are also varied (Table 2) and require some level of standardization.

Nevertheless, despite these limitations, aortic input impedance provides a comprehensive, frequency-dependent view of afterload encountered by the heart and may facilitate a more personalized approach to HTN by delineating what pathophysiological factors are involved in each patient. Thus far, the existing literature lends support for the role of Z_0, Z_1 and f_0 in essential HTN, although additional studies and standardizations are needed before input impedance can be confidently applied to the clinical setting.

ACKNOWLEDGEMENTS

This research was supported by grant number P30AT005895 of the National Center for Complementary Alternative Medicine (NCCAM). The project described was supported by Clinical Translational Science Award UL1RR025758 to Harvard University and Massachusetts General Hospital from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Complementary Alternative Medicine or the National Center for Research Resources or the National Institutes of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The manuscript represents our original work and has not been published previously in print or electronic format. All authors for this manuscript meet criteria for authorship. No author has any affiliation with an organization with financial interest in the material presented in this manuscript.

Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

This review aims to quantify the relevance of aortic input impedance in hypertension, with the aim to provide a more comprehensive assessment of the arterial load on the heart beyond the measurement of arterial blood pressure. This was assessed by analysis of studies that measured input impedance in human subjects. Although the final analysis was in a relatively small number of studies, the relative impedance components were peripheral resistance, impedance at heart rate frequency and frequency of zero phase. The greater variability and reduced significance of characteristic impedance was essentially due to the difficulty in obtaining reliable non-invasive flow measurements.

Reviewer 2

This is the first study to summarize all presently available publications on input impedance in controls and hypertensive patients. Hypertensive patients have increased resistance and modulus at first harmonic, but aortic characteristic impedance is not different from controls. The impedance data are compared with systolic, diastolic and mean pressure.

The Authors have not tried to obtain information on arterial stiffness, an arterial parameter of importance. The implications and explanations why relations are (not) found with pressure are not explained. The general reader is left wondering what impedance, as comprehensive description of the arterial system, can be most informative about arterial function.