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Energetically wasteful wave reflections due to impedance mismatching in hypertension and their reversal with vasodilator: Time and frequency domain evaluations

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ABSTRACT

Background: Increased pulse wave reflections in hypertension arise due to impedance mismatching and the effective energy transmission to the vasculature is compromised. Their quantification in the time and the frequency domains are compared and the beneficial effect of vasodilator is evaluated in the study.
Methods: A simple, fast time domain method for the resolution of aortic pressure and flow pulses into their forward and reflected components is presented, together with frequency domain reflection coefficient and impedance calculations. Both steady and pulsatile energy components are quantified during induced hypertension (HBP) and subsequent vasodilator (VSD, nitroprusside) treatment in experimental mongrel dogs. Corresponding power generation and usage are also analyzed.
Results: Characteristic impedance and peripheral resistance were not statistically different between the methods ($p > 0.05$). Time domain reflection coefficient identified significant differences among control, HBP and VSD groups ($p < 0.05$) while the frequency domain method did not adequately differentiate the control and the HBP groups. Impedance calculations were similar between the two methods. Frequency domain calculations of total, mean and pulsatile power were, on average, 32.6 mW higher, 12.8 mW lower and 45.4 mW higher than their respective time domain calculations ($p < 0.05$). Hypertension increased energy consumption, on average, by 88.8 mJ ($p < 0.05$) and subsequent VSD decreased the energy consumption, on average, by 99.4 mJ ($p < 0.05$).
Conclusion: Impedance mismatching in hypertension which leads to increased wave reflections and significantly increased pulsatile work, could be effectively alleviated through vasodilator therapy. This can be quantified through the time-domain method, which is fast and equally accurate as the time-consuming frequency domain approach. The time domain method to quantify crucial parameters such as stroke work cannot be readily determined using the frequency domain methods.

1. Introduction

Vital organs of the human body are perfused as a consequence of pulsations in pressure and flow generated with each cardiac contraction. The shapes of the propagating pressure and flow pulses in the arterial system are dependent on the arterial wall properties and the vasoactive states. Their pulsatile waveforms can be explained in terms of incident and reflected waves. These component waves can provide information on the interaction of the central vessels and the peripheral vasculature. Such interaction is heavily dependent on the amount of stroke work generated by the heart and the effective transmission of the pulsatile energy which in turn is dependent on the extent of impedance matching.

In terms of the classic transmission line theory [1–4], the magnitude of pulse wave reflection can be computed from the measurement of impedances. For a single uniform line with characteristic impedance, Z_o terminated with a load impedance Z, the amount of forward propagating wave (Pf) that is reflected (Pr) is given by the reflection coefficient:

$$\Gamma = \frac{Z - Z_o}{Z + Z_o} \quad (1)$$

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It is also the ratio of forward and reflected waves, along with their respective amplitudes and phases,

$$\Gamma = \frac{P_r}{P_f} \tag{2}$$

The reflection coefficient so obtained is, therefore, a complex quantity with magnitude and phase varying with frequency. For the arterial system, Z_o is the characteristic impedance of the proximal aorta, and Z is the input impedance of the arterial tree. Z_o has been shown to have a weak dependence on frequency and thus has been assumed to be resistive only [5,6].

The characteristic impedance, Z_o, by definition is independent of reflections [7], as it is an attribute of the aorta [8], and is given by

$$Z_o = \frac{P_f}{Q_f} = -\frac{P_r}{Q_r} \tag{3}$$

Here, the negative sign indicates that reflected pressure and reflected flow are 180° out of phase i.e. a decrease in blood flow will increase the reflected pressure if Z_o is maintained constant.

While Z can be obtained easily from the harmonic ratios of pressure and flow, the accurate measurement of Z_o is, in general, a difficult task. Many investigators have thus estimated the magnitude of Z_o from the average of the high-frequency components of the input impedance modulus. This is based on the assumption that at high frequencies, the pulse is greatly attenuated, and the associated propagating wavelengths are short such that peripheral reflections cannot reach the proximal aorta in any significant amount. In the frequency domain, Z_o has been approximated from the high-frequency average of Z, i.e. 3rd to 10th harmonic [4]. Westerhof et al. and others [9–12], took this approach to resolve aortic waveform into its forward and reflected components. It requires digitization and subsequent Fourier transform.

A fast time-domain method to resolve the pressure pulse into its forward and reflected components, originated by Li in 1986 [13], is now widely used. This approach assumes that the peripheral reflections do not reach the proximal aorta in any appreciable amount in the early part of systole. Wave separation has become a necessary step in understanding the contributions of wave reflections to hypertension [14–17]. Hence, comparison of time and frequency domain determinations of characteristic impedance becomes imperative in order to verify their respective accuracy [18–22] and to resolve the blood pressure and the flow waveforms into their respective forward and reflected components [23–25].

The reflection of the propagating pulse wave indicates that the wave encounters impedance mismatching and therefore energy is wasted through power dissipation along the vasculature. The present investigation sets out to quantify the stroke work and pulsatile energy generated by the heart under normal conditions and to evaluate how they are altered in hypertension. We also examine how the popularly used vasodilator therapy can enhance more efficient pulsatile power transfer. A comparison of the time-domain method with the frequency domain method for quantifying wave reflections and other quantities that describe the energy perspectives of the arterial system is also presented.

2. Methods

2.1. Separation of forward and reflected waves and the reflection coefficient

The amplification of pressure pulses has been attributed to the in-phase summation of reflected waves arising from structural and geometric non-uniformities. Iliac bifurcation and the renal arterial branches at the abdominal aorta have been recognized as the principal reflection sites [26]. Thus, pulsatile pressure and flow waveforms contain information about the heart as well as the vascular system. Reflection in the vascular system has been suggested as a closed-end type, with arterioles being the major reflection site. Reflected pressure and flow waves are 180° out of phase. This means an increase in reflection increases pressure amplitude but decreases flow amplitude.

Measured pressure (P) and flow (Q) waveforms measured at any site in the vascular system can be considered as the summation of a forward, or antegrade, traveling wave and a reflected, or retrograde, traveling wave:

$$P = P_f + P_r \tag{4}$$

$$Q = Q_f + Q_r \tag{5}$$

The forward and reflected pressure components can be resolved by means of the following set of equations:

$$P_f = \frac{P + QZ_o}{2} \tag{6}$$

$$P_r = \frac{P - QZ_o}{2} \tag{7}$$

where Z_o is the characteristic impedance, defined as the ratio of forward pressure to forward flow, or in other words, independent of wave reflections, as shown above (eqn. (2)). With the characteristic impedance determined by a time domain method, forward and reflected waves can also be obtained in the time domain [13].

Similarly, resolution of flow into its forward and reflected components can be obtained from a set of two equations [18].

$$Q_f = \frac{Q + \frac{P}{Z_o}}{2} \tag{8}$$

$$Q_r = \frac{Q - \frac{P}{Z_o}}{2} \tag{9}$$

The characteristic impedance is determined in the time-domain as an average value during the very early part of systole [11,12,13,25]:

$$Z_o = \frac{P(t) - P_d}{Q(t)} \tag{10}$$

The reflection coefficient is defined as the harmonic ratio of reflected wave to the forward wave in the frequency domain:

$$\Gamma = \frac{|P_r|\angle\Phi_f}{|P_f|\angle\Phi_r} \tag{11}$$

It has both a modulus and a phase, and varies with frequency:

$$\Gamma = |\Gamma|\angle\Phi \tag{12}$$

This means that the reflection coefficient is dependent on the amplitude (magnitude) and the arrival time (phase) of the reflected wave with respect to the forward traveling wave. The reflection coefficient thus obtained in the time domain is compared to the frequency domain computations, given in eqn. (1) above.

2.2. Steady and pulsatile energy considerations

Stroke work (W) for each heartbeat or the external work of the left ventricle or the total energy is obtained, for the entire cardiac cycle as:

$$W = \int_0^T P(t)Q(t)dt \tag{13}$$

$$W = Ws + Wp \tag{14}$$

Where P(t) and Q(t) are aortic pressure and flow, respectively. It has a steady energy component, Ws and a pulsatile energy component, Wp. The former is defined as the product of mean arterial pressure (P_m) and stroke volume (SV) while the latter is dependent on the pulsatile pressure and flow waveforms and in turn wave reflections. Pm can be estimated by integrating the pressure signal over the cardiac cycle and

then the integral value was divided by the heart period. (T).

$$P_m = \frac{1}{T}\int_0^T P(t)dt \tag{15}$$

$$SV = \int_0^T Q(t)dt \tag{16}$$

$$W_s = P_m.\ SV \tag{17}$$

$$W_p = W - W_s \tag{18}$$

The instantaneous power for each heartbeat at any time can be calculated as:

$$\boldsymbol{P(t)} = P(t).\ Q(t) \tag{19}$$

The steady flow mean power is the product of mean aortic pressure and mean aortic flow:

$$\boldsymbol{Pm} = Pm.\ Qm \tag{20}$$

And the in-phase oscillatory or pulsatile power is calculated from impedance (Zn) and flow (Qn) harmonics:

$$\boldsymbol{Po} = \frac{1}{2}\sum_{n=1}^{N} Z_n \cdot Q_n^2 \cdot cos\theta_n \tag{21}$$

where Θ is the angle between pressure and flow harmonics.

2.3. Experiments and data collection

Experiments were performed on normal mongrel dogs after Rutgers University IACUC Approval. A left thoracotomy was performed on each dog after the induction of Nembutal anesthesia with an intravenous bolus of 30 mg/kg. An electromagnetic flowmeter and a Millar catheter were placed at the same site in the ascending aorta. The Millar catheter was pushed forward through the femoral artery while the electromagnetic flowmeter was placed after isolating a segment of the ascending aorta. Furthermore, Lead II electrocardiogram (ECG) was recorded to identify the beginning of the pressure cycle and the flow cycle. Recordings were made at steady-state, at control conditions and during intravenous administration of 2–5 mg/ml methoxamine (MTX), a potent vasoconstrictor that induces hypertension (HBP) and subsequent infusion of 50 μg/ml nitroprusside (NTP) induced vasodilation (VSD). In total, 11 recorded aortic pressure and flow datasets (5 control, 3 hypertensive and 3 vasodilator) were sampled at 100 Hz from 5 dogs and were stored for computational analysis.

2.4. Computations and data analysis

The computations were performed using MATLAB 2017b software run on a MacBook Pro with a 2.6 GHz Intel Core i5 processor. In order to calculate the Fourier spectrum of impedance, reflection coefficient, and pulsatile energy, the Fast Fourier Transform algorithm was used to obtain complex estimates. Energy and power units were converted to SI unit by using the following factor: 1 mmHg ml = 1333.33 μJ. The computation of energy and power involved the following steps:

Step 1: The measured aortic pressure was resolved into its forward and reflected components (equations (6) and (7)) using the Z_0 that was calculated from the time domain equation (10).
Step 2: The measured aortic flow was then resolved into its forward and reflected components using equations (8) and (9).
Step 3: Stroke Work or energy (W) was calculated by integrating the product of measured aortic pressure and flow signals using the trapezoidal method after interpolating the measured signals to 1 μs time resolution. The forward and reflected energies were also computed similarly from the resolved components of aortic pressure and flow using equation (13) in which the pressure and the flow signals are substituted by their respective components.
Step 4: The steady component of energy or stroke work Ws was computed from the product of stroke volume and mean arterial pressure. The stroke volume was quantified by integrating the flow signal after interpolation to 1 μs time resolution through the trapezoidal method. The mean arterial pressure was calculated by adding together the diastolic pressure and one-third of the pulse pressure.

The pulsatile energy component, Wp, is the difference between total stroke work W and the steady energy component Ws (eqn. (18)).

Step 5: Instantaneous power **P(t)** was computed as the point-to-point product of the measured aortic pressure and flow signals. Forward and reflected instantaneous powers were calculated from the resolved components of the aortic pressure and flow signals.
Step 6: Total power **P** was calculated in the frequency domain as the sum of mean power **Pm** and pulsatile power **Po** where **Pm** was calculated as the product of the square of absolute value of flow and the absolute value of impedance at 0 Hz while **Po** was calculated as half the sum of product of square of the absolute value of flow, the absolute value of impedance and the cosine of the phase of impedance at all harmonics. (eqn. (21)). In the time domain, the total power **P** was calculated as the integral of **P(t)** after interpolating the signal to 1 μs and then the integrated value was divided by the heart period. The mean power **Pm** was calculated as the product of mean pressure and mean flow (eqn. (19)). and the pulsatile power **Po** was calculated as the difference between **P** and **Pm**.

2.5. Statistical analysis

The computed parameters were statistically analyzed with mean, standard deviation and one-way ANOVA and Pearson's Correlation. Post-hoc analysis of the results of one-way ANOVA was performed using the Tukey-Kramer test. All the statistical tests were performed with $p < 0.05$ taken as the level of significant difference.

3. Results

Table 1 summarizes the hemodynamic parameters of the experimental subjects. Intravenous infusion of MTX resulted in significantly increased pressure, both systolic ($p = 0.003$) and diastolic ($p = 0.003$), as well as mean pressure ($p = 0.003$) with a slower heart rate

Table 1
Hemodynamic parameters of experimental subjects.

Group	Systolic Pressure (mmHg)	Diastolic Pressure (mmHg)	Mean Arterial Pressure (mmHg)	Pulse Pressure (mmHg)	Heart Rate (beats/min)	Stroke Volume (ml)
Control Group						
Mean	119.8	94.8	104.6	25.0	138.0	8.9
std	9.7	9.1	10.2	1.2	17.5	0.3
HBP Group						
Mean	173.3	139.0	149.4	34.3	118.5	10.9
std	23.4	13.9	16.6	8.1	20.1	4.3
p-value[a]	0.003	0.003	0.003	0.096	0.323	0.485
VSD Group						
Mean	93.8	63.3	71.7	30.5	155.3	12.4
std	9.9	13.6	10.9	3.8	4.6	1.0
p-value[b]	0.098	0.018	0.017	0.379	0.398	0.153
p-value[c]	< 0.001	< 0.001	< 0.001	0.658	0.072	0.714

HBP = Methoxamine induced hypertension and VSD = Nitroprusside induced vasodilation.
[a] Comparison between the hypertension group and the control group.
[b] Comparison between the vasodilation group and the control group.
[c] Comparison between the vasodilation group and the hypertension group.

Table 2
Comparison of time and frequency domain methods calculations of aortic characteristic impedance, peripheral resistance and reflection coefficient. HBP = Methoxamine induced hypertension and VSD = Nitroprusside induced vasodilation.

Group	Frequency Domain			Time Domain		
	Z_o [mmHg s ml^{-1}]	Rs [mmHg s ml^{-1}]	Γ (1st harmonic)	Z_o [mmHg s ml^{-1}]	Rs [mmHg s ml^{-1}]	Γ (1st harmonic)
Control Group						
Mean	0.223	5.331	0.607	0.209	5.331	0.464
Std	0.098	0.654	0.161	0.027	0.654	0.051
HBP Group						
Mean	0.198	8.326	0.717	0.189	8.326	0.643
std	0.028	4.069	0.196	0.037	4.069	0.075
p-value[a]	0.912	0.191	0.618	0.776	0.191	0.015
VSD Group						
Mean	0.198	2.314	0.145	0.194	2.314	0.147
std	0.061	0.571	0.085	0.053	0.571	0.080
p-value[b]	0.908	0.187	0.009	0.861	0.187	< 0.001
p-value[c]	1.000	0.020	0.005	0.988	0.020	< 0.001

[a] Comparison between the hypertension group and the control group.
[b] Comparison between the vasodilation group and the control group.
[c] Comparison between the vasodilation group and the hypertension group.

(p = 0.248) and statistically insignificant changes in stroke volume in comparison with the control group. The increase in pulse pressure was also statistically insignificant. In contrast to the HBP group, vasodilator administration resulted in significantly decreased diastolic and mean pressure (p = 0.018 and p = 0.017 respectively). The decrease in systolic and pulse pressure, the increase in heart rate and the increase in stroke volume were statistically insignificant compared to the control group. However, the VSD group had significantly lower systolic, diastolic and mean pressure in comparison to the hypertensive group. Pulse pressure, heart rate, and stroke volume changes were statistically insignificant.

Table 2 shows the calculated peripheral resistance and the characteristic aortic impedance in both time domain and frequency domain. Peripheral resistance is the same value, as expected, in both time domain and frequency domain as the steady flow power of the measured aortic pressure and flow signals at 0 Hz frequency always equals the mean aortic pressure and the mean aortic flow values respectively. One-way ANOVA resulted in statistically insignificant difference with p = 1 and a correlation of r = 1 (p < 0.001) between the two estimation methods. The characteristic aortic impedance was found to be numerically different, albeit similar, between the two estimation techniques (see Fig. 1 for the mean difference and the limits of agreement). The one-way ANOVA resulted in a statistically insignificant difference with p = 0.628 and a correlation of r = 0.421 (p = 0.198) was found between the two methods of impedance estimation. Peripheral resistances and characteristic impedances of the HBP and the VSD groups were not significantly different from the control group. However, the use of vasodilator to treat hypertension resulted in insignificant characteristic impedance change (p = 0.988 in the time domain and p = 1.000 in the frequency domain) and lower peripheral resistance (p = 0.020) compared to the hypertension group.

The numerical difference in characteristic impedance and peripheral resistance resulted in different reflection coefficients amongst the three groups (see Fig. 2 for the mean difference and the limits of agreement). It is also worth noting that the reflection coefficient in the hypertensive state is higher than that in the normotensive state (p = 0.618 and p = 0.015 from the frequency domain and the time domain methods) and the reflection coefficient in the vasodilated state

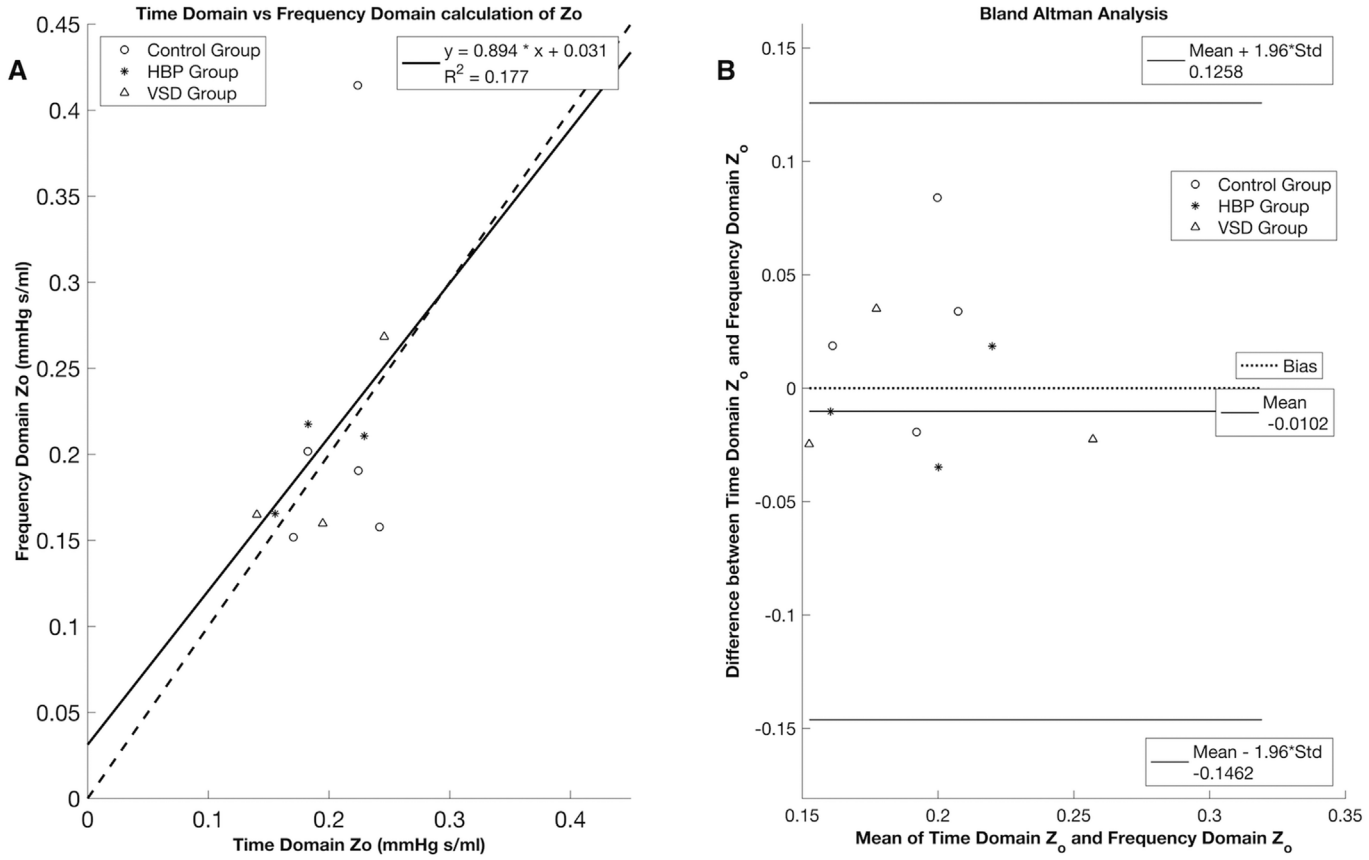

Fig. 1. A Comparison of estimation of the characteristic impedance of the aorta using time domain and frequency domain methods. The line of identity is also shown (dotted line). **B** Bland Altman Analysis between the time domain and the frequency domain estimations of the characteristic impedance.

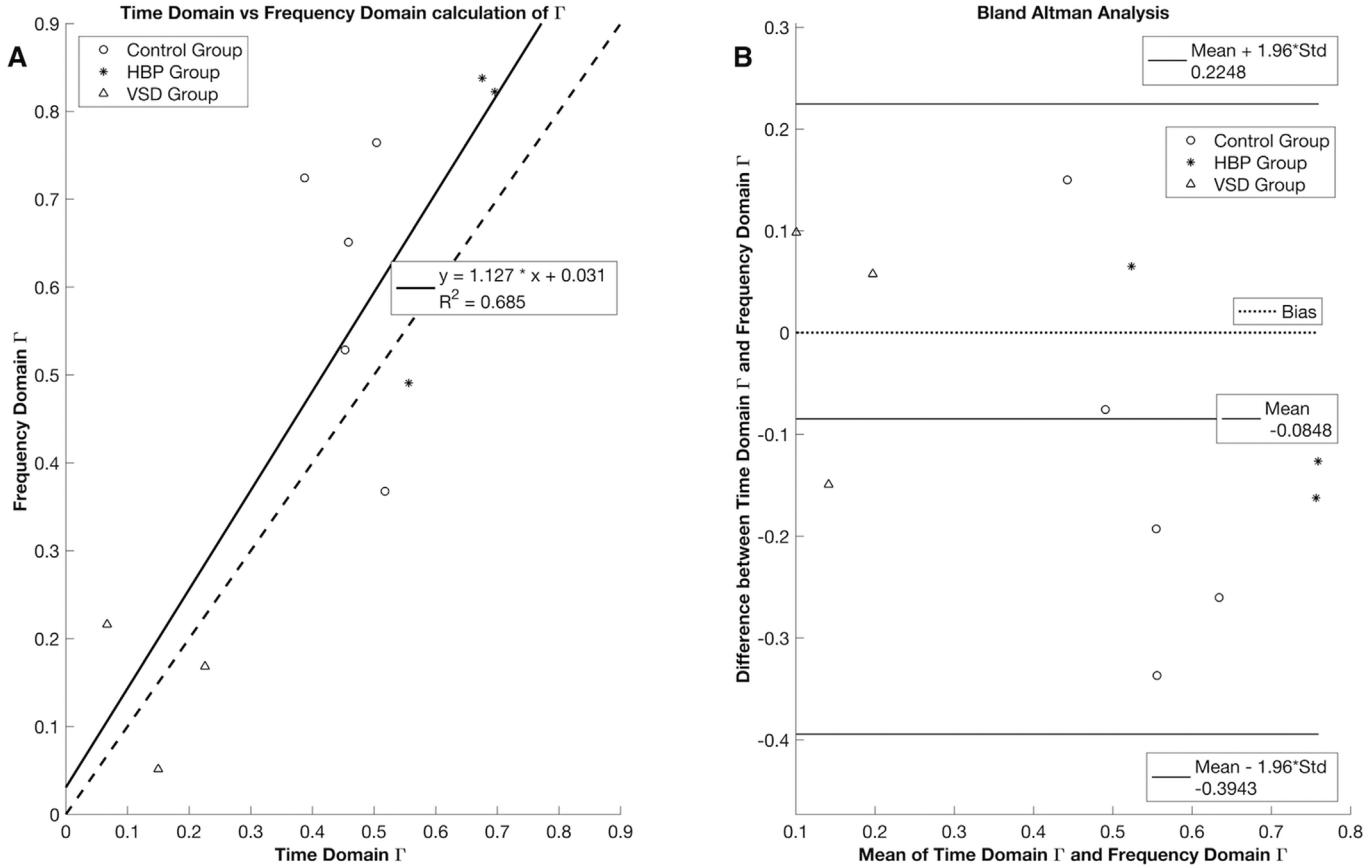

Fig. 2. A Comparison of estimation of reflection coefficient using time domain and frequency domain methods. The line of identity is also shown (dotted line). **B** Bland Altman Analysis between the time domain and the frequency domain estimations of the reflection coefficient.

is lower than that in the normotensive state ($p = 0.009$ and $p < 0.001$ from the frequency domain and the time domain methods). Moreover, vasodilation reduced the wave reflections that were high due to increased pressure ($p = 0.005$ and $p < 0.001$ from the frequency domain and the time domain methods). Furthermore, the reflection coefficients that were calculated using the time domain method were lower than those values that were computed using the frequency domain method for the normotensive and hypertensive cases (see Table 2) while the reflection coefficient for the vasodilated cases had very similar values. One-way ANOVA between the time domain and the frequency domain methods resulted in a statistically insignificant difference ($p = 0.106$) and a correlation of $r = 0.827$, $p = 0.002$ was found between the two methods of estimation.

Fig. 3 shows the representative resolved forward and reflected components of the measured aortic flow and aortic pressure for each group. The reflected pressure waves are higher during acute hypertension and lower after vasodilator administration. Moreover, the reflected pressure wave arrives earlier in systole in acute hypertension and later with vasodilator infusion. It is also clear that the forward and the reflected waves are similar in magnitude during diastole as the aortic valve is closed. The resolved flow components behave similarly to the pressure waves in terms of magnitude, except that more negative reflected flow is found with greater wave reflection.

Fig. 4 shows the frequency domain input impedance to the arterial tree. The plot reveals that 0 Hz impedance or the peripheral resistance Rs is higher in acute hypertension and lower during vasodilator administration, as expected (see Table 2). The phase is more negative during hypertension, and the phase being more negative implies decreased capacitance. The phase oscillates around zero during vasodilation and that indicates an increased capacitive component of impedance. The plots also show the distribution of impedance over the first ten harmonics whose average values are shown in Table 2. The changes in phase reflect the change in quadrant (or sign) of the imaginary component in the frequency domain and this does not affect the absolute value that characterizes the aortic impedance.

The total energy required by the heart to overcome the arterial load through stroke work for each group is shown in Fig. 5. It is unambiguous that hypertensive hearts have to work more than the normal hearts and that the action of vasodilators reduces the work to be done by the hearts. The resolution of the pulsatile pressure and flow waves manifests the energy produced by the heart that propels the blood forward (forward energy) and the energy reflected along the vasculature. The normal hearts used 128.4 ± 15.6 mJ of energy to overcome the impedance with a total forward energy of 232.3 ± 25.5 mJ while 105.6 ± 20.1 mJ was reflected along the vasculature. On the other hand, the hypertensive hearts used 215.9 ± 66.1 mJ ($p = 0.1441$ vs control) of energy to overcome the peripheral resistance with a total forward energy of 544.5 ± 120.0 mJ ($p = 0.419$ vs control) while 335.8 ± 55.5 mJ (0.0125 vs control) was reflected along the vasculature. The use of vasodilators reduced the energy that was used by the heart (122.4 ± 21.9 mJ, $p = 0.123$ vs HBP) to normal levels with a total forward energy of 156.2 ± 44.5 mJ ($p = 0.0201$ vs HBP) while 32.7 ± 35.0 mJ ($p = 0.0026$ vs HBP) was reflected along the vasculature. The VSD group reflected less energy than the control group.

The instantaneous power that was calculated from the aortic pressure and flow signals of representative cases are shown in Fig. 6. The plot indicates that the induced hypertension group generates more power than the control group and this increased power generation is reduced by the vasodilator therapy. The time domain and the frequency domain calculations of total power and mean power that had been used by the heart showed no significant differences among the groups. The total forward power generated by the heart was 2043.4 ± 435.3 mW,

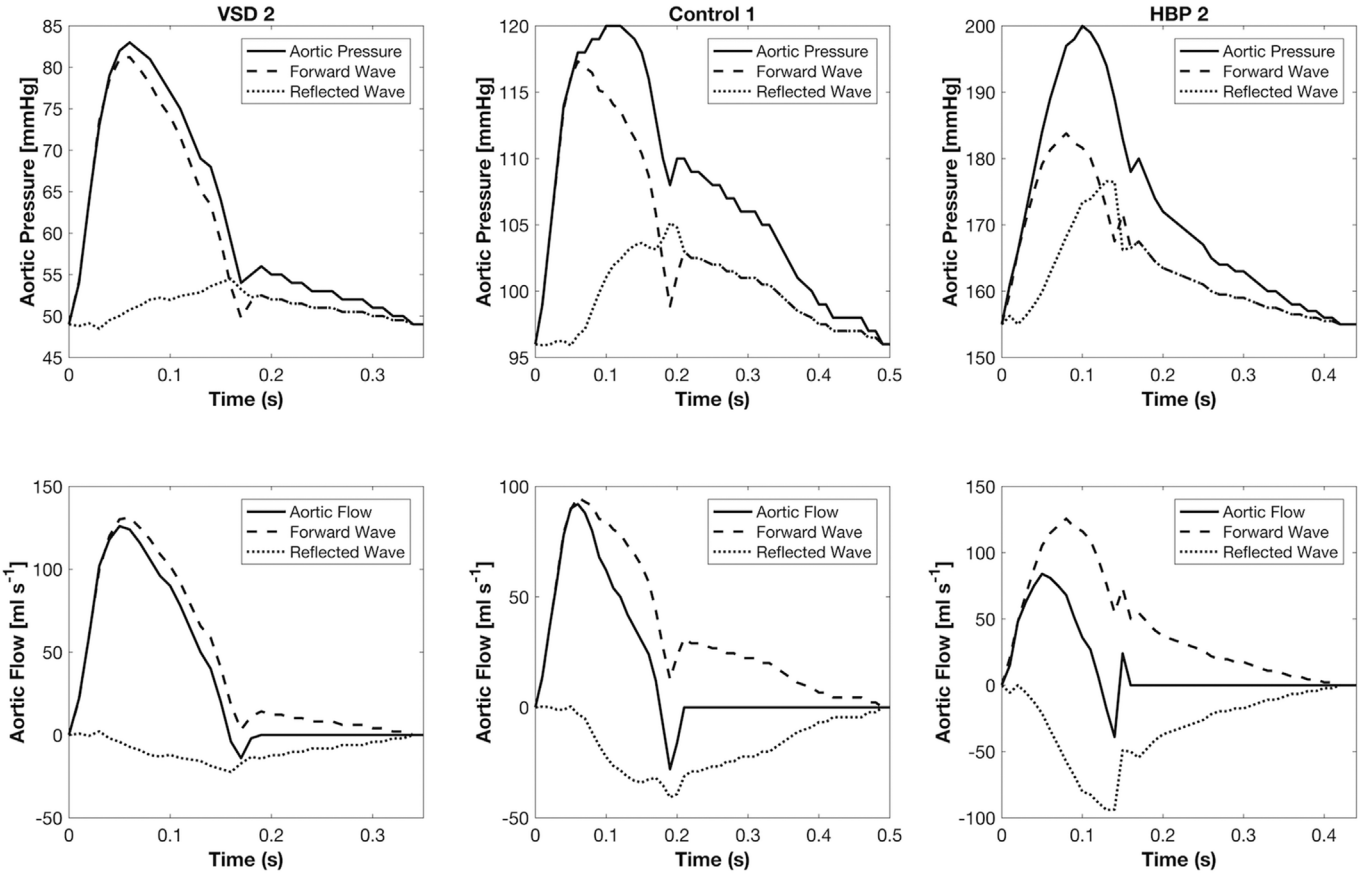

Fig. 3. Sample data illustrating measured aortic pressure and aortic flow signals that have been resolved into their respective forward and reflected waves.

4383.0 ± 615.9 mW and 1277.1 ± 580.5 mW of which 1719.0 ± 368.6 mW, 3941.4 ± 550.1 mW and 894.5 ± 573.2 mW was reflected along the vasculature. The frequency domain method of calculation resulted in higher total power for all datasets (see Table 3) with a statistically significant difference ($p < 0.001$) and a correlation of $r = 0.991$ ($p < 0.001$) was found. However, the time domain method of calculation resulted in higher mean power for all the datasets with a statistically significant difference ($p < 0.001$) and a correlation of 0.999 ($p < 0.001$). Pulsatile power calculations from both the methods resulted in a significant difference between the VSD group and both the control and the HBP groups. But there was no significant difference between the control and the HBP groups. Furthermore, the frequency domain method resulted in significantly higher pulsatile power compared to the time domain method ($p < 0.001$) with a correlation of 0.977 ($p < 0.001$).

4. Discussion

An increase in pulse pressure is often associated with increased wave reflection, which in turn has been attributed to increased arterial stiffness. Both increased peripheral resistance and arterial stiffness augment input impedance that comprises the arterial load which makes the heart work harder to maintain the stroke volume. This is often observed in chronic hypertension. Thus, wave reflection serves as an indicator of pulsatile arterial load to the heart. It has been quantified through the reflection coefficient in the frequency domain and it is calculated from the measured pressure and flow waveforms based on the impedance method, as shown in the present study. The amount of wave reflection has also been accounted for in the time domain by the separation of pressure and flow into forward and reflected waves, as presented in the study. Results from the present experimental study show that the two methods are well correlated and the differences between the methods were statistically insignificant in terms of estimating characteristic impedance or the amount of wave reflections. Bland-Altman analysis of the methods shows the limits of agreement between the methods and this difference can be attributed to the uncertainty in determining the characteristic impedance. The non-uniformities in large and small elastic arteries and geometric properties (e.g. branching and tapering) are encompassed by the frequency domain input impedance, particularly in its oscillations. These frequency domain oscillations are attributed to the variable reflected waves, also due to elastic and geometric mismatching. However, the time domain method is simpler and faster to use in the clinical setting than the frequency domain method to quantify the wave reflections. Furthermore, the time domain reflection coefficient had significant differences among all groups while the frequency domain method failed to differentiate the hypertension group from the normal group.

Increased reflection coefficients of the HBP group (Table 2) result in higher energy generation and expenditure per beat (Fig. 5). In the present study, the hypertensive group generates almost twice the energy as the normal group. The action of the vasodilator decreases the reflection coefficient (see Table 2). Decreased wave reflections result in less stroke work which brings the energy generated by the heart similar to the control group. The decrease in external work compared to the hypertensive group is due to a decrease in peripheral resistance that is caused by profound dilation of the peripheral arteries, in addition to significantly reduced wave reflections. The latter resulted in significantly less reflected energy. The reason for such a distinct difference between the control group and the vasodilator group is the reduction in pressure, an increase in stroke volume and faster heart rates. Thus, the total external work done by the heart is similar even when the pressure and stroke volume ranges are different.

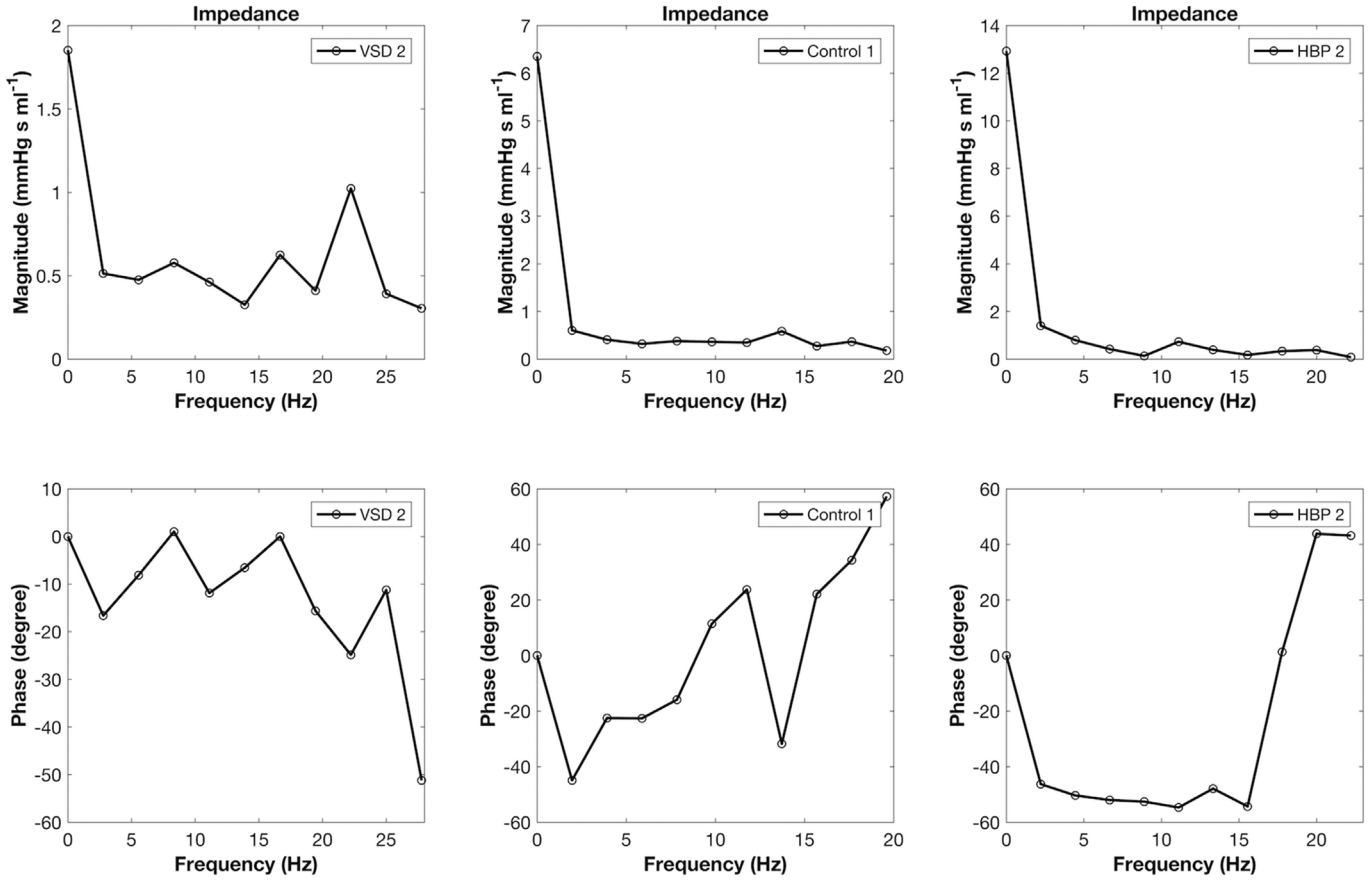

Fig. 4. Representative magnitude and phase plots of input impedance of control, hypertensive and vasodilator cases. Note that the high-frequency average of impedance modulus is used to estimate the characteristic impedance.

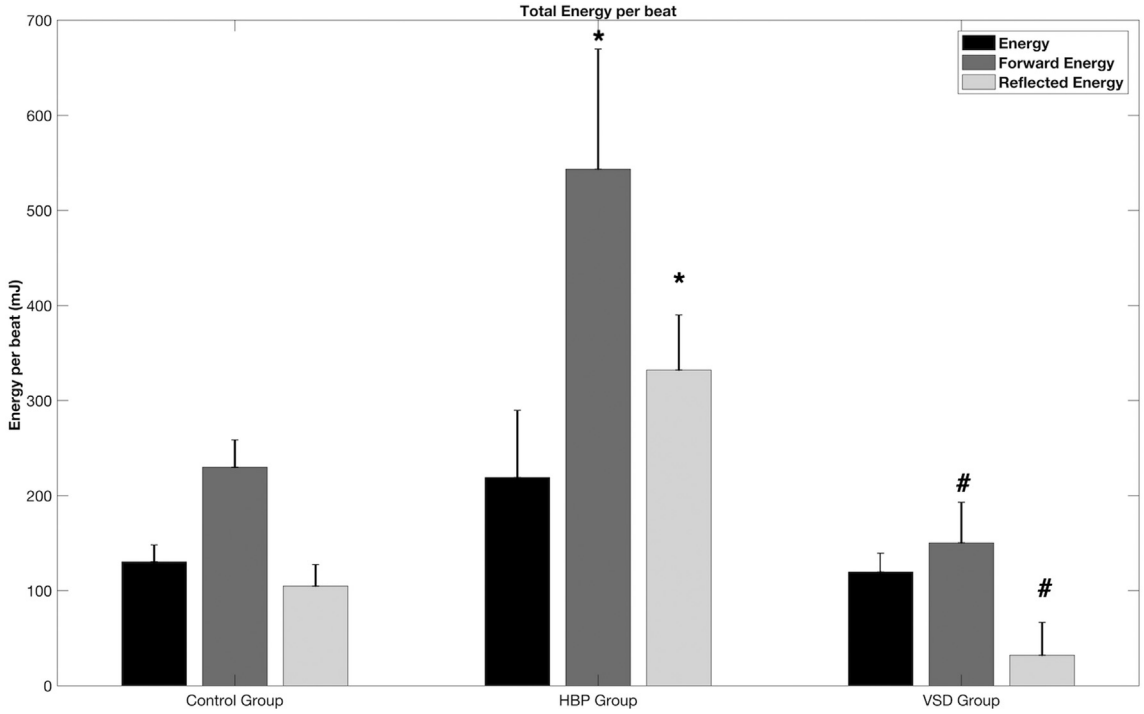

Fig. 5. Forward and reflected energy components during control, hypertension and vasodilation. A significant difference ($p < 0.05$) is shown with * between HBP and control and # between VS and HBP.

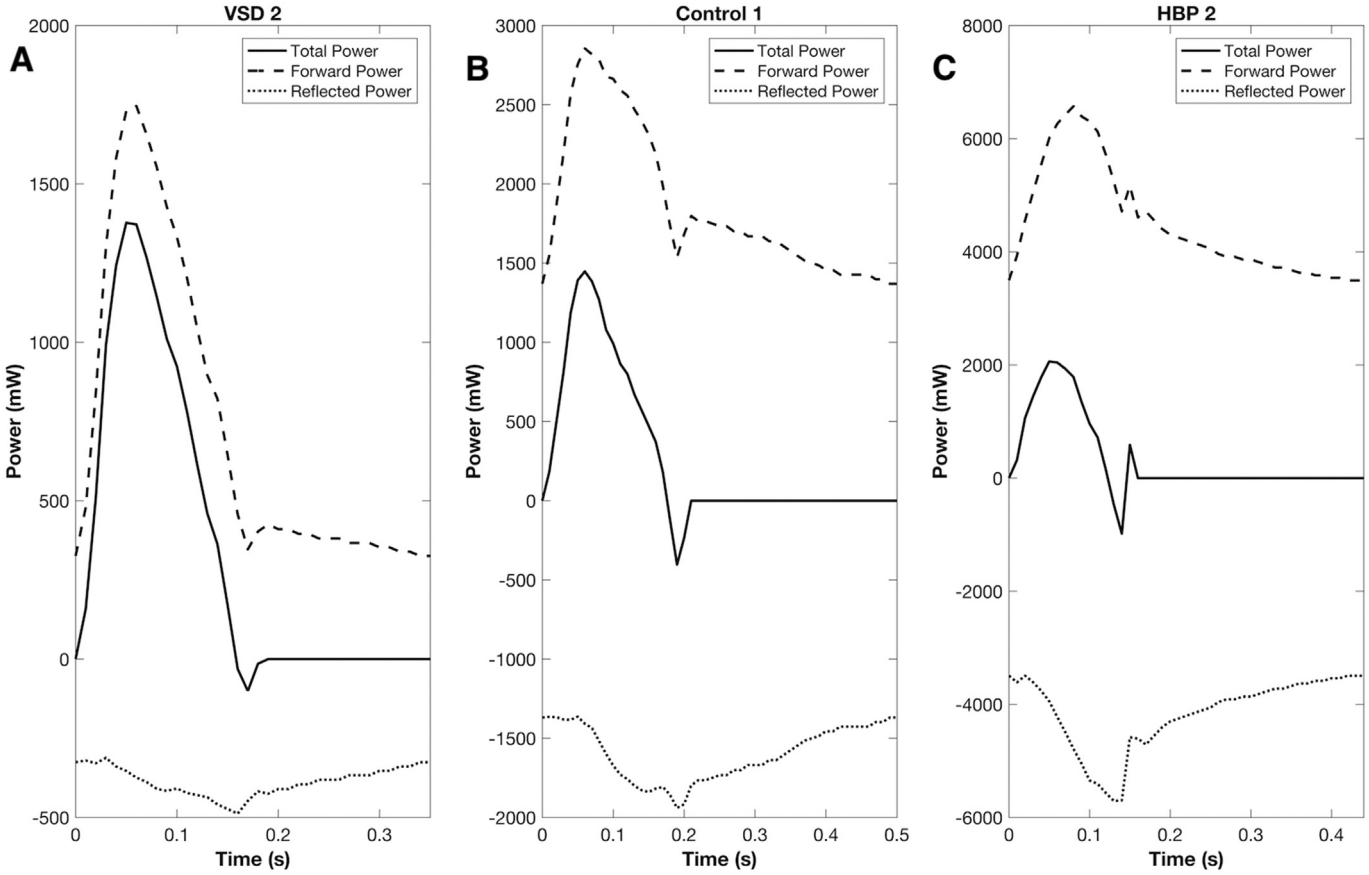

Fig. 6. Representative instantaneous power generated by the heart under control, hypertensive and vasodilator treated conditions.

Table 3
Calculated Total Power in the Time Domain and Frequency Domain (including the mean and in-phase pulsatile powers).

Group	Time Domain			Frequency Domain		
	Total Power (mW)	Mean Power (mW)	Pulsatile Power (mW)	Total Power (mW)	Mean Power (mW)	Pulsatile Power (mW)
Control Group						
Mean	324.4	304.7	19.7	346.5	290.5	56.0
std	73.3	71.4	1.8	74.0	67.1	7.3
HBP Group						
Mean	441.6	423.8	17.8	471.9	407.0	64.9
std	129.5	126.6	2.9	132.2	124.6	9.4
p-value[a]	0.228	0.206	0.934	0.201	0.200	0.648
VSD Group						
Mean	382.6	316.9	65.6	434.9	310.3	124.5
std	37.4	35.9	13.5	39.5	37.1	22.1
p-value[b]	0.657	0.980	< 0.001	0.415	0.944	< 0.001
p-value[c]	0.705	0.336	< 0.001	0.873	0.380	0.001

HBP = Methoxamine induced hypertension and VSD = Nitroprusside induced vasodilation.
[a] Comparison between the hypertension group and the control group.
[b] Comparison between the vasodilation group and the control group.
[c] Comparison between the vasodilation group and the hypertension group.

When the time domain method and the frequency domain method to compute ventricular power are compared, the difference in all the power components computed must be taken into account. There is a distinct difference between the total power, the mean power and the pulsatile power computed from the two methods (both statistically and numerically). This can be traced back to the definition of power in the frequency domain method. Mean power is defined as the 0 Hz harmonic power of the pressure and the flow signals. This is mathematically the statistical average of the samples of both signals. Meanwhile, the time domain method uses the mean pressure and flow calculated by integrating the signals over the entire cardiac cycle. They are mathematically different, and the frequency domain method depends on the sampling rate. It should also be noted that the time domain method is susceptible to numerical integration error. However, it should be negated by interpolating the signal to low time scales. The oscillatory or pulsatile power, **Po (**eqn. (21)) considers only the in-phase or cosine components while the time domain method directly computes pulsatile power and instantaneous power from measured aortic pressure and flow waveforms.

Another important aspect of the present study lies in the translation of the results from the dog model to human physiology. Even though dogs have different characteristic impedance, peripheral resistance, and heart rate, the aortic pressure and the aortic flow waveforms are similar and the impedance harmonics, the reflection harmonics, and the power plots are roughly comparable [27]. Much earlier studies by other investigators showed that administration of norepinephrine, a potent vasoconstrictor, increased the power during systole [28]. The systolic power calculated from our study also shows an increase in power during acute hypertension induced with methoxamine, also a potent vasoconstrictor. This increased power was reversed when the potent vasodilator nitroprusside was infused (see Fig. 6). Acute hypertension also caused increased impedance and heart rate similar to another study [29]. The increased wave reflections result in pulsatile energy being lost which has not been shown in previous studies [28–30]. Furthermore, the action of vasodilator unloads the heart by reducing the energy lost. This unloading is particularly visible in mid-to-late systole.

Consideration of the pulsatile nature of blood flow in clinical assessment has been commonplace. Wave intensity analysis, introduced by Parker [31,32], has been used to study the reflection phenomenon of

the pulse wave. This method computes the wave intensity as a sum of intensities of wavelets and assumes no linearity or periodicity on the part of the arterial system. Even though non-linearity is prescribed in the one-dimensional flow equations that are used to calculate wave intensities, the assumptions for the resolution of components in this method results in similar impedance calculations. While the wave intensity method could be used to compute energy flux, the time domain method described in this paper can calculate the total energy (both useful and wasteful) and the total power that the arterial system uses. However, the wave intensity method is useful in calculating the distance of the reflection sites. The application of the time domain method described in the present study lies in quantifying reflections.

In addition to the wave intensity analysis, there are some studies that infer a limited role for the reflected wave under conditions that increase pulse pressure [33–35]. Torjesen et al. [33] and Li et al. [34] advance the idea that change in ventricular ejection or contraction increases the pulse pressure while Vennin et al. [35] state that the reflection wave characteristics are negligible at pulse pressure. It should also be noted that Torjesen at al. used the augmentation index to develop the linear model based on wave morphology and Li et al. used the ratio of the waves in the time domain as the reflection ratio. Augmentation index calculated based on inflection pressure tend to be close to zero at both vasoactive states because of the definition of the inflection pressure when the arterial compliances tend to be in different states. The reflection ratio from Li et al. is beyond the scope of this research. However, Li et al. conclude that arterial reflections are affected when the vascular muscle tone is affected by Nitroglycerine. Our results also show that vasodilation significantly reduces reflections. Furthermore, methoxamine and nitroprusside affect the systemic pressure through peripheral effects. Their direct effects on the heart seem to be minimal [36,37]. Vennin et al. also discuss the error in central pressure prediction during early systole under the assumption of zero or limited reflections. This shows the need for future validation studies to determine the acceptable clinical limits of predictions with models that assume the propagation of pressure waves and zero or limited reflections.

Recent research in right ventricular stroke work has revealed the need for accounting the pulsatile nature of the pulmonary vasculature [38]. The methods described in the present study can be easily incorporated for pulmonary hypertension treatment through the calculations of reflections and stroke work and access the impact of a specific drug on pulmonary vasculature. Other methods using the principal component analysis based on linear transforms have also come up with an index based on the pulsatile component as a risk factor for coronary artery disease [39]. The separation of steady flow and pulsatile flow energy utilization, as presented here, has been less common but it is shown here to be pertinent in evaluating the state of the external work of the heart.

The time domain method described in the present paper can aid in future clinical studies to better understand the mechanics of blood flow in a specific group of interest. Input impedance that represents the complex vascular load in terms of its structural properties [40–42] such as characteristic impedance, arterial compliance, and peripheral resistance, can exert significant influences on the energy utilization associated with the propagating pulse. As we demonstrated in the present study, wave reflections result in the wasteful use of pulsatile energy.

The beneficial effect in the use of vasodilators is clearly demonstrated here in its ability to revert the wasteful energy consumption due to induced hypertension. It is likely that other anti-hypertensive drug therapies beyond nitrates, such as beta-blockers, calcium channel-blockers, and angiotensin-converting enzyme inhibitors can also bear such overall and pulsatile energy-reduction benefits through reduction of wave reflections, as we have demonstrated here.

4.1. Limitation of the study

We recognize that the small sample size for each of the three groups in this experimental study is a limitation. This, for instance, is seen in the large standard deviation of peripheral resistance in the hypertensive group. The data presented here nevertheless serve to differentiate hemodynamic and energetic differences. With a larger pool of experimental or clinical data, we believe we will arrive at similar conclusions.

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