

Nitric Oxide Is Released Into Circulation With Whole-Body, Periodic Acceleration*

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Study objective: To determine if comfortably applied, whole-body, periodic acceleration releases significant amounts of nitric oxide (NO) into the circulation of healthy subjects and patients with inflammatory diseases.

Materials: Fourteen healthy adults and 40 adult patients with inflammatory diseases underwent single 45-min trials of whole-body, periodic acceleration with a new “passive exercise” device, while an ECG and a digital pulse wave were obtained with a photoelectric-plethysmograph sensor.

Methods: The position of the dicrotic notch from the pulse waveform was computed from the amplitude of the pulse divided by the height of the dicrotic notch above the end-diastolic level (*a/b* ratio). Increase of the *a/b* ratio reflects the vasodilator action of NO that causes downward movement of the dicrotic notch in the diastolic limb of the digital pulse, thereby elevating the *a/b* ratio.

Results: Application of whole-body, periodic acceleration was well tolerated in all participants, and all completed the 45-min treatment. The peak value of the *a/b* ratio markedly rose during periodic acceleration and returned to baseline during a 5-min recovery period in all healthy subjects and patients with inflammatory diseases.

Conclusions: Whole-body, periodic acceleration increased pulsatile shear stress to the endothelium leading to vasodilatation and a fall in the dicrotic notch, consistent with increased NO bioactivity in every healthy adult and adult patient with inflammatory disease so treated. Therefore, passive exercise using whole-body, periodic acceleration produces an important benefit that occurs with active exercise. (CHEST 2005; 127:30–39)

Key words: dicrotic notch; endothelial nitric oxide synthase; nitric oxide

Abbreviations: *a/b* ratio = amplitude of pulse wave divided by height of dicrotic notch above the end-diastolic level; cGMP = cyclic guanosine monophosphate; eNOS = endothelial nitric oxide synthase; NO = nitric oxide

Passive exercise signifies movement of the limbs or body of a subject who does not or cannot exert volitional control of the appropriate skeletal muscles. It can be accomplished with a motorized bicycle, a tandem bicycle with one rider pedaling while the other rider passively relaxes to allow the legs to move on the other pedals, or through passive leg extensions in a chair apparatus. Since such “passive exer-

ise” devices do not improve hemodynamics as does active exercise, their designation as “exercise” devices might be questioned.^{1–3} One of the most important benefits of active exercise in health and disease is nitric oxide (NO) released into the circulation through activation of endothelial NO synthase (eNOS) owing to increased shear stress to the endothelium. NO generated from eNOS has direct vasodilator and antiatherosclerotic properties as well as indirect antiinflammatory and antitumorigenic actions mainly due its suppression of nuclear factor- κ B,

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the key transcriptional gene for inflammatory mediators.^{4–8} If a passive exercise device could be shown to release significant amounts of NO, then passive exercise might enjoy credibility as a therapeutic modality.

The present study deals with a newly introduced passive exercise device that is based on whole-body, periodic acceleration. Increased amounts of NO are released into the circulation from activation of eNOS when laminar or pulsatile shear stress to the endothelium takes place. Laminar shear stress is associated with increased blood flow, whereas pulsatile shear stress has been shown in isolated blood vessels to be optimally effective within a frequency of about 180 to 360 pulses per minute.⁹ Periodic acceleration promotes release of NO from eNOS within isolated porcine aorta as well as anesthetized pigs at 240 cycles per minute and $\pm 3.9 \text{ m/s}^2$ by adding sinusoidal pulses to the circulation because fluid shifts occur with each acceleration and deceleration.^{10–12}

In preliminary trials, the speed and gravitational settings for whole-body, periodic acceleration utilized in anesthetized animals was too vigorous to be tolerated by adult volunteers. Therefore, in the current study in humans, an approximately 50% reduction of speed and acceleration in meters per second squared was employed. Evidence that NO is released into the circulation during application of whole-body, periodic acceleration was inferred by observing the dicrotic notch or wave position of the finger pulse. Descent of either the dicrotic notch or wave down the diastolic limb occurs because NO dilates resistance vessels, thereby delaying pulse wave reflection. The purpose of this study was to ascertain whether the lower speed and gravitational settings for whole-body, periodic acceleration in humans compared to animals still releases significant amounts of NO into the circulation. Healthy subjects and patients with inflammatory diseases¹³ were selected for the trial. Such patients were enrolled because on the known antiinflammatory properties of NO released from eNOS.

MATERIALS AND METHODS

Subjects

Acute Study of Dicrotic Notch Position During Therapeutic Periodic Acceleration Settings: Twelve healthy men and 2 healthy women (mean age, 44 years; SD, 14 years) and 19 male and 21 female patients (mean age, 64 years; SD, 15 years) were enrolled in this study. The diagnoses comprised osteoarthritis of hip and knees (n = 11), Parkinson disease (n = 5), multiple sclerosis (n = 3), peripheral neuropathy (n = 2), carpal tunnel syndrome (n = 1), restless legs syndrome (n = 1), COPD (n = 1), bronchial asthma (n = 1), fibromyalgia (n = 2), fibromyalgia and bronchial asthma (n = 1), chronic fatigue syndrome and fibromyalgia (n = 1), chronic fatigue syndrome (n = 1), pulmonary fibrosis

(1), pulmonary hypertension and congenital single ventricle (n = 1), coronary artery disease after coronary artery bypass grafts (n = 3), coronary artery disease with pacemaker (n = 1), post-stroke spasticity (n = 1), chronic venous insufficiency (n = 1), interstitial cystitis (n = 1), and post-polio syndrome (n = 1). The medications prescribed by the patients' physicians were not changed for the study. Two of the four patients with coronary artery disease were receiving organic nitrates and β -blockers.

Acute Study of Dicrotic Notch Position During "Sham" Periodic Acceleration: Three healthy men and two healthy women, and one man and one woman with osteoarthritis participated in this study. The medications prescribed by the patients' physicians were not changed for the study.

Methods

The Institutional Review Board of Mount Sinai Medical Center of Greater Miami approved the study protocol, and written informed consent was obtained from all participants. None of the subjects received financial remuneration for their participation. Because of extremity movements during whole-body, periodic acceleration, venipunctures are difficult to perform. Therefore, it was not considered ethical to draw bloods for serum nitrite determinations during periodic acceleration in noncompensated volunteers.

Whole-body, periodic acceleration was accomplished with a motion platform device that has a gurney-like appearance driven by a two-flywheel motor assembly. It has a handheld controller that regulates cycles per minute and acceleration. The supine subject lies on a mattress onto the motion platform for repetitive head-to-foot movements delivered at approximately 140 cycles per minute and approximately $\pm 2.2 \text{ m/s}^2$ (Acceleration Therapeutics AT101; Non-Invasive Monitoring Systems; North Bay Village, FL). The device is 222 cm long, 77.5 cm wide, and weighs 211 kg. A foot board, 112 cm high, for strapping the subject's feet enclosed in shoes is utilized to couple the body to the motion platform during periodic acceleration. The motion platform is capable of moving subjects up to 150 kg in body weight at rates between 60 cycles and 200 cycles per minute and up to $\pm 3.9 \text{ m/s}^2$.

Descent of the dicrotic notch or wave of the digital pulse down the diastolic limb reflects the vasodilator action of NO on the resistance vessels owing to delay in pulse wave reflection. This phenomenon has been noted with endothelial-independent preparations of organic nitrates as well as with endothelial dependent agents such as albuterol and terbutaline, β -adrenergic agonists that act through the NO pathway. The change of dicrotic notch or wave position is computed by measuring the amplitude of the digital pulse wave divided by the height of the dicrotic notch or wave above the end-diastolic level (a/b ratio); alternately, the height of the dicrotic notch or wave above the end-diastolic level divided by the amplitude of the digital pulse wave ratio may be reported.^{14–18} In the current study, the dicrotic notch rather than the dicrotic wave was utilized to compute the a/b ratio since the peak of the reflective wave particularly at baseline was usually difficult to detect in elderly subjects (Fig 1).

During whole-body, periodic acceleration, the added pulses and motion artifacts usually prevent visual detection of the dicrotic notch position. Therefore, it is necessary to employ an ECG R-wave-triggered, ensemble-averaging computer program routine to reveal the dicrotic notch of the digital pulse and eliminate the added pulse waves. Trial and error indicated that a three to seven heart beat average was a reliable means to obtain a normal-appearing pulse waveform, although in some patients ensemble-averaging was unnecessary (Fig 2). To aid in detection of the dicrotic notch, the second derivative of the ensemble-

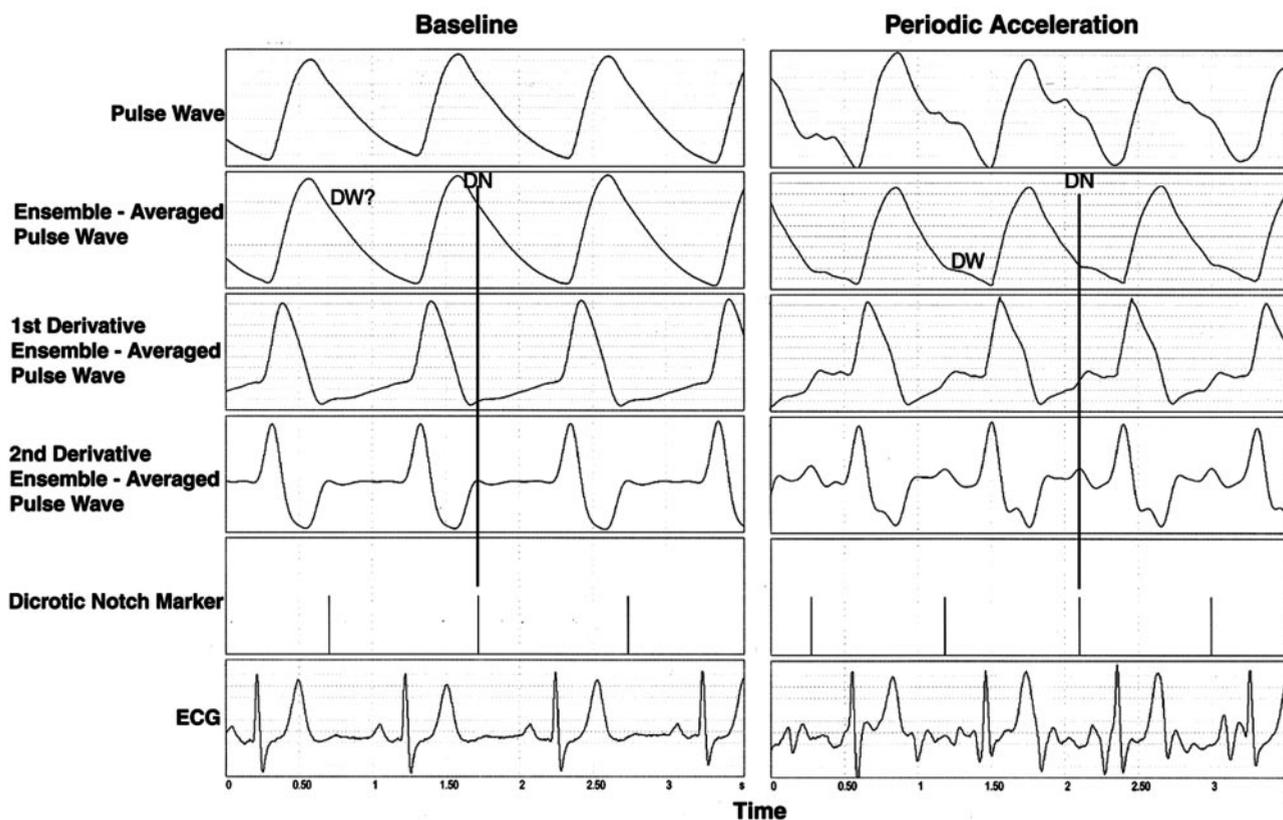


FIGURE 1. Dicrotic notch (DN) and dicrotic wave (DW) in an asymptomatic patient with coronary artery disease several years after coronary bypass surgery. The following traces of the digital pulse are depicted: the raw pulse wave; five-beat, ensemble-averaged pulse wave, and its first and second derivatives; and the dicrotic notch marker. The latter occurs at the peak of a positive deflection wave during diastole of the second derivative of the pulse wave. Each pulse wave of the ensemble-averaged pulse represents an average of the five preceding pulses. At baseline, it is difficult to visualize the dicrotic notch and impossible to discern the dicrotic wave. During periodic acceleration, small pulsations are superimposed on the raw pulse wave with a spurious appearance of a dicrotic notch; the five-beat ensemble-averaged pulse reveals a consistent dicrotic notch much lower than its spurious appearance in the raw pulse wave with an indistinct peak of dicrotic wave.

averaged pulse wave was displayed and the peak of its largest upward deflection in diastole was taken as the point for the dicrotic notch. The computer program calculated the a/b ratio based on this algorithm. If the end-diastolic level moved to the next pulse waveform as judged by an end-diastolic level higher than the dicrotic notch (Fig 3), then an arbitrary value of 100 was assigned to the a/b ratio; otherwise, the value would be indeterminate. The value of 100 was selected because the highest calculated values of the a/b ratio were 96, 96, and 97 in three subjects in whom the dicrotic notch fell within the same pulse, respectively. The computer-aided detection point for dicrotic notch position required confirmation by an observer who could visually adjust the timing of its position if there was disagreement. The added pulses to the circulation during whole-body, periodic acceleration also prevented auscultatory cuff BP measurements.

In 11 healthy subjects and 5 patients, the respiration recorder (Respirace PT; Non-Invasive Monitoring Systems), which incorporates a three-lead ECG with R-wave trigger pulse and a pulse oximeter (Minx; Ohmeda; Louisville, CO), was used to record the effects of a 45-min trial of periodic acceleration. The pulse wave from the pulse oximeter of this device was set to a 3-s average with a digital sampling rate of 50 points per second. The RS232 output of this device was inputted into a personal computer

(Inspiron 4000; Dell; Austin, TX) for recording of the raw and ensemble-averaged digital pulse waveforms and dicrotic notch detection algorithm. In three healthy subjects and 35 patients, the respiration recorder (Respirace 202; NonInvasive Monitoring Systems) was used to record the effects of periodic acceleration. This device incorporates a three-lead ECG with R-wave trigger pulse and an input for receiving an analog signal from a photoelectric-plethysmograph pulse waveform (model 2122i Bioamplifier; UPI; Morro Bay, CA) that was digitized at 200 points per second. The RS232 output of the Respirace 202 was inputted into a personal computer (Inspiron 4000) for recording of the raw and ensemble-averaged digital pulse waveform and dicrotic notch detection algorithm. The ensemble-averaged pulse was displayed as a continuous scalar trace, such that each beat represented an average of the number of pulse waves preceding the ensemble. There was no difference between the two devices for obtaining the digital pulse wave with regard to changes in the a/b ratio during whole-body, periodic acceleration.

Study Design

Twelve healthy men and 2 women, and 19 male and 21 female patients underwent a single 45-min trial of whole-body, periodic

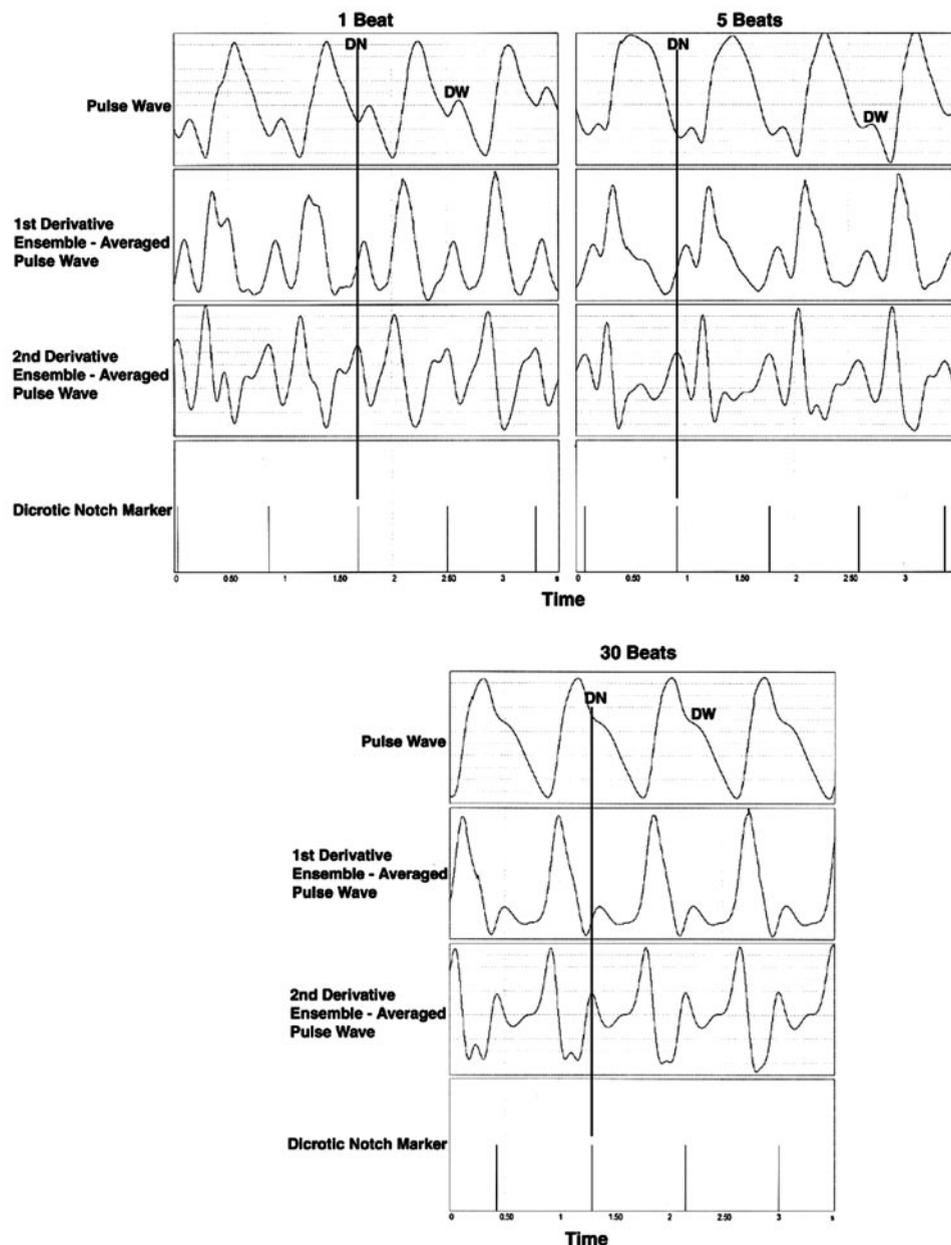


FIGURE 2. Effects of the number of beats in ensemble-average depicting pulse wave traces in a patient with Parkinson disease. The following traces of the digital pulse are depicted: the raw pulse wave, ensemble-averaged pulse wave and its first and second derivatives, and the dicrotic notch marker. The latter occurs at the peak of a positive deflection wave during diastole of the second derivative of the pulse wave. In this patient, added pulses were not superimposed on the natural pulse probably because of low arterial compliance. The raw pulse wave (not shown) and the one-beat ensemble-averaged pulse wave were identical in appearance. The one-beat trace shows a rising dicrotic notch and dicrotic wave. The five-beat average also depicts this phenomenon with less prominent dicrotic wave. The 30-beat average completely eliminates the dicrotic notch rise and suppresses dicrotic wave. This damping of the oscillations of the true dicrotic notch behavior with 30 beats as depicted in the one-beat average occurs because it produces a mean value rather than a peak value. See Figure 1 legend for expansion of abbreviations.

acceleration with therapeutic settings of approximately ± 2.2 m/s², and approximately 140 cycles per minute. This produces horizontal platform displacement of approximately 2 cm. The therapeutic settings were obtained from pilot studies in three healthy subjects and two patients with osteoarthritis that revealed

acceptable subject comfort and noticeable descent of the dicrotic notch of the digital pulse. Three healthy men and two healthy women, and one male and one female patient also underwent a single 45-min trial of “sham” whole-body, periodic acceleration with settings of approximately ± 0.5 m/s², 120 to 140 cycles per

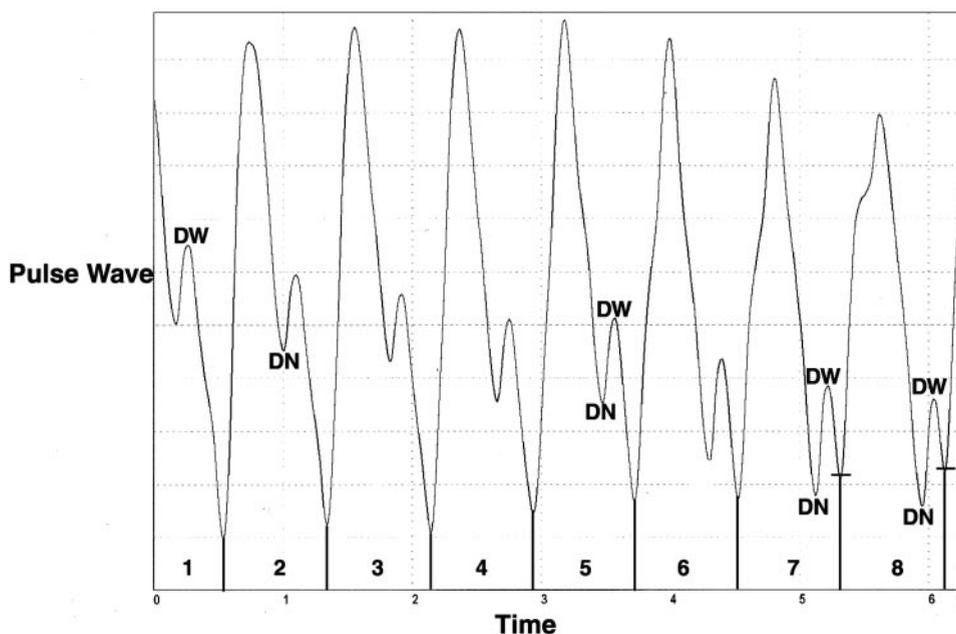


FIGURE 3. Dicrotic wave and end-diastolic level moving into next pulse wave in the same patient as depicted in Figure 2, with display of the raw pulse wave. The vertical lines at the bottom of the trace indicate end-diastolic levels. Beats one to six show almost progressive descent of dicrotic wave and dicrotic notch. Beats seven and eight show movement of part of the dicrotic wave and end-diastolic level into next pulse wave. See Figure 1 legend for expansion of abbreviations.

minute, which caused approximately 3 mm of horizontal displacement. Three-lead ECG electrodes were placed on the chest, and a reusable photoelectric plethysmograph sensor was put on the index finger. The lead II ECG and the digital pulse waveform were recorded for a 3- to 5-min baseline period, during 45 min of whole-body, periodic acceleration, and for a 3- to 5-min recovery period. The mean values for heart rate and the peak values for the a/b ratio were measured off-line for the three time intervals.

Statistical Analysis

Statistical analysis of the data was accomplished with a statistical software package (Statistica 6.0; StatSoft; Tulsa, OK). Results are expressed as mean (SD), and comparison of means was carried out using analysis of variance followed by *post hoc* analysis with the Newman-Keuls test. Significance between means was taken as $p < 0.05$.

RESULTS

The application of whole-body, periodic acceleration was well tolerated over the 45-min period in all healthy adults and adult patients; everyone completed the full treatment time without interruption. All extremities and the body repetitively and passively moved during whole-body, periodic acceleration, thereby fulfilling the definition of “passive exercise.” The dicrotic notch position of the ensemble-averaged pulse wave descended down the diastolic limb of the digital pulse wave causing the a/b ratio to rise (Fig 4). In 6 of the 40 patients (15%) who

were > 65 years old, the dicrotic notch position could be distinguished in the raw pulse wave during periodic acceleration (Fig 5). As depicted in these figures, the a/b ratios usually showed sustained periods of cyclic rise and fall toward baseline values during whole-body, periodic acceleration. Descent of the dicrotic notch usually began within 15 to 25 s of the institution of periodic acceleration. A peak value of the a/b ratio of 100 signified that the end-diastolic level had moved into the next pulse wave (Fig. 3). This phenomenon occurred in 6 of the 14 healthy subjects and 16 of the 40 patients during whole-body, periodic acceleration. If the values for subjects with a/b ratio of 100 were excluded from the mean, then for 8 healthy subjects the mean baseline peak a/b ratio was 1.9 (SD, 1) and during periodic acceleration was 16.2 (SD, 3.7); for the 24 patients, the corresponding values were 1.6 (SD, 1.1) and 36.2 (SD 4.4), respectively. As listed in Table 1, in both healthy adults and patients, there was a large rise of the peak a/b ratio during whole-body, periodic acceleration followed by an immediate fall toward baseline in the recovery period. The increase of peak a/b ratio was of similar magnitude in both the healthy adults and patients. The mean heart rate showed a significant increase of 12 beats/min during periodic acceleration in the healthy subjects but did not significantly change in the patients. The mean heart rate was 63 beats/min (SD, 9) at baseline and 60

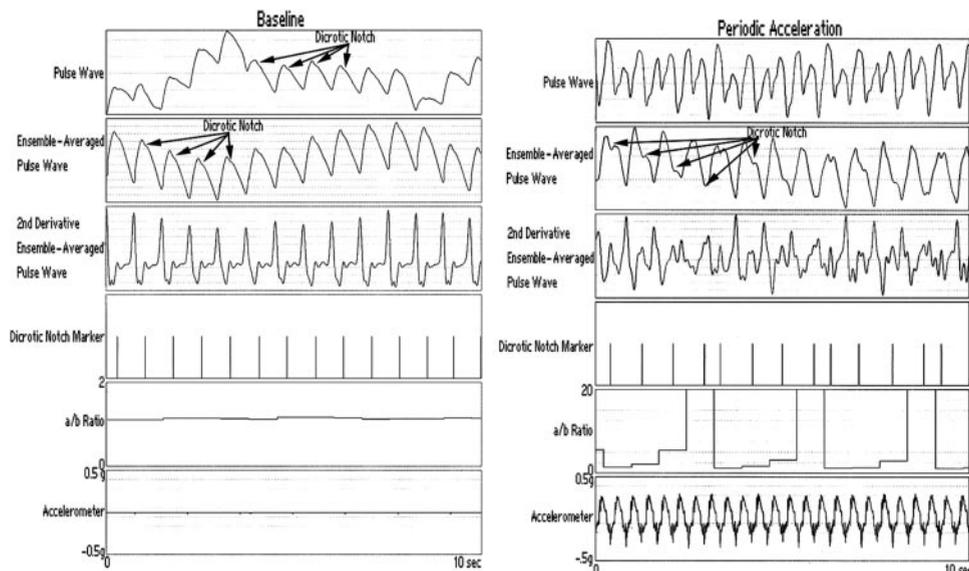


FIGURE 4. Cyclic variation of the dicotic notch in a patient with fibromyalgia. *Left*: Pulse wave and the seven-beat, ensemble-averaged pulse wave at baseline. Each pulse wave of the ensemble-averaged pulse represents an average of the seven preceding pulses. The dicotic notch is marked as the peak, large upward deflection in diastole of the second derivative of the ensemble-averaged waveform. The a/b ratio is computed on a pulse-by-pulse basis. *Right*: During whole-body, periodic acceleration, added pulses obscure the dicotic notch position of the pulse wave. The ensemble-averaged pulse depicts cyclic variation of the dicotic notch position and a/b ratios. The latter is a trace that automatically depicts a/b ratios on a beat-by-beat basis.

beats/min (SD, 10) during sham periodic acceleration ($p > 0.05$) in five healthy subjects and two patients with osteoarthritis. Corresponding peak a/b ratio values were 1.3 (SD, 0.2) and 1.3 (SD, 0.2), respectively ($p > 0.05$).

DISCUSSION

This study indicates that whole-body, periodic acceleration is well tolerated and associated with release of NO into the circulation as reflected by downward descent of the dicotic notch of the digital pulse wave. The association of fall in the dicotic notch with organic nitrates was first described by Morikawa et al^{19,20} in 1967 in dynamite factory workers exposed to nitroglycerin and ethylene nitrate. These investigators²¹ subsequently noted this phenomenon in volunteers who drank beer as an alcoholic beverage. Since alcohol activates eNOS to release NO,²² probably alcohol caused vasodilatation and downward descent of the dicotic notch through a NO pathway. In rabbits, descent of the dicotic notch occurs after administration of acetylcholine, an endothelium-dependent activator of eNOS.²³

Descent of the dicotic notch of the pulse wave appears to be due to a specific dilating action of NO on the resistance blood vessels that produces delayed arrival of the pulse wave to the site and delayed

return of the reflected wave. The latter accounts for the creation of the dicotic notch. It is quantified with the a/b ratio; some investigators report the height of the dicotic notch or wave above the end-diastolic level divided by the amplitude of the digital pulse wave ratio. With either ratio, a dose response to NO donor drugs has been observed.^{17,24}

In terms of peak response of the a/b ratio, whole-body, periodic acceleration produces far higher values than organic nitrate preparations that release NO or albuterol and terbutaline that act through a NO pathway. The peak a/b ratio in the current study increased 2,200% in healthy adults and 3,775% from baseline in the patients with inflammatory diseases. The two lowest increases in peak a/b ratio were 145% and 173% from baseline in healthy adults and 235% and 300% from baseline in patients. Values of the a/b ratio for the digital pulse by photoelectric plethysmography or radial pulse by applanation tonometry provided in the literature or by computation of the a/b ratios of pulse waves depicted in articles after the administration nitroglycerin, albuterol, or terbutaline in various forms was reviewed. Nitroglycerin in therapeutic sublingual, spray, ointment, and transdermal patch doses increased the a/b ratio from 26 to 89%.^{14,16,18,25-31} Chowienczyk et al¹⁴ found the highest peak increase of the a/b ratio, 205% in an adult receiving nitroglycerin, 0.1 mg IV,

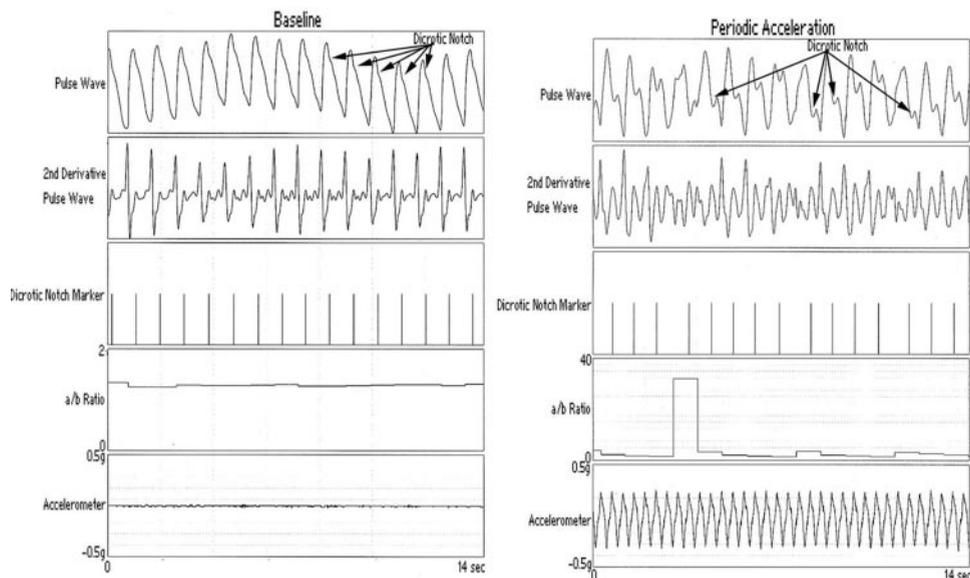


FIGURE 5. Cyclic variation of the dicrotic notch in a patient with bronchial asthma. *Left*: Pulse wave and the second derivative at baseline. *Right*: Pulse wave during whole-body, periodic acceleration, in which the absence of added pulses during periodic acceleration presumably is due to reduced compliance of the digital artery so that the dicrotic notch position can be identified without resorting to ensemble averaging. This recording shows cyclic variation of the dicrotic notch position in the pulse wave and the a/b ratio traces.

and 124% in an adult receiving albuterol, 20 $\mu\text{g}/\text{min}$ IV. Since changes of the a/b ratio from the action of NO follow a dose-response curve, whole-body, periodic acceleration appears to be much more potent in accessibility to NO than organic nitrates or β -adrenergic agonists in terms of vasodilatation of the resistance vessels.

Shift of the dicrotic wave and end-diastolic level into the next pulse wave during whole-body, periodic acceleration occurred in 6 of the 14 healthy subjects and 16 of the 40 patients. Morikawa et al²⁰ observed this phenomenon in a dose-response study of ethylene nitrate in humans. With increasing doses of this compound, the dicrotic notch descended down the diastolic limb of the finger pulse. At the highest dose, the dicrotic wave and end-diastolic level moved into the beginning of the next pulse (Fig 3).²⁰ When this phenomenon occurs, calculation of the a/b ratio

becomes indeterminate. Since the highest a/b ratios for three subjects in the current study equaled 96, 96, and 97, respectively, it was decided to arbitrarily assign a value of 100 to observations in which the diastolic wave and end-diastolic level moved into the next pulse as being close to a value that had been calculated in the same pulse. Even if such values are excluded from the mean, the a/b ratio rose 750% from baseline in healthy subjects and 2,160% in patients, still much greater than reported for NO donor drugs or β -adrenergic agonists as mentioned above.

Whole-body, periodic acceleration adds pulses to the circulation because fluid shifts occur within the body as the motion platform accelerates and decelerates.^{11,32} Hutcheson and Griffith⁹ perfused rat aorta segments with Holman solution that contained indomethacin using a peristaltic pump. The effluent

Table 1—Effect of Whole-Body, Periodic Acceleration on Peak a/b Ratio and Heart Rate*

Participants	Baseline Peak a/b Ratio	Periodic Acceleration Peak a/b Ratio	Recovery Peak a/b Ratio	Baseline Heart Rate, beats/min	Periodic Acceleration Heart Rate, beats/min	Recovery Heart Rate, beats/min
Healthy subjects (n = 14)	2.3 (1.0)	53 (44)‡	3.3 (1.5)	64 (11)	76 (10)†	62 (10)
Patients (n = 40)	1.6 (.5)	62 (39)‡	2.0 (1.0)	70 (12)	73 (12)	67 (13)

*Data are presented as mean (SD).

†p < 0.01 difference between periodic acceleration value and baseline and recovery values.

‡p < 0.001 difference between periodic acceleration value and baseline and recovery values.

was measured for endothelium-derived relaxing factor now known to be NO by a bioassay technique. Endothelial-derived relaxing factor values were a function of the frequency of flow pulsations through the aorta. Peak response occurred between 250 cycles and 360 cycles per minute, but there was still good response between 180 cycles and 210 cycles per minute. Adams et al¹² recently perfused isolated porcine aortas with nonpulsatile, pulsatile, and pulsatile flow plus periodic acceleration. NO at the effluent site was measured with a NO electrode. Pulsatile flow increased NO, reported as nitrite, relative to nonpulsatile flow 300% and periodic acceleration applied to the pulsatile flow model caused a 1,000% increase relative to steady flow. This large increase of nitrite emphasizes the potent effect of periodic acceleration. Descent of the dicrotic notch with whole-body, periodic acceleration occurred in all patients in the current study, even those who might have been expected to have endothelial dysfunction such as elderly patients and those with coronary artery disease.

It was not possible to measure BP noninvasively during whole-body, periodic acceleration because the natural pulse wave could be distinguished from the added pulses. There were no added pulses observed on the digital plethysmographic pulse wave in 15% of the elderly patients possibly because of reduced arterial compliance. Intravascular recordings of arterial pressure in anesthetized pigs indicate that mean BP falls 10 mm Hg during periodic acceleration.¹¹ If BP also falls in humans during periodic acceleration, then an increased heart rate should occur from activation of the baroreceptor reflex. In the healthy adults, a significant rise of heart rate of 12 beats/min took place but the heart rate did not rise in the patients. The reason for this difference might be that the patients were older than the healthy subjects and had diseases known to be associated with impaired sensitivity of the baroreceptor reflex, such as coronary artery disease, neurodegenerative diseases, fibromyalgia, and chronic fatigue syndrome, and in two instances taking of β -blockers.^{33,34}

In this investigation of whole-body, periodic acceleration, NO release from eNOS was surmised because of previous isolated blood vessel and animal findings of NO release with periodic acceleration.¹² A literature review that was performed by searching the National Library of Medicine database using the terms "dicrotic notch," "dicrotic wave," "pulse wave," and "digital plethysmograph" failed to find any reports of dicrotic notch descent unrelated to the action of NO. Indexes based on the descent of the dicrotic notch and wave have both been used to assess the action of NO on the resistance ves-

sels.^{16,17,35} Lund¹⁶ measured both indexes and found that they tracked each other after nitroglycerin administration. The changes of dicrotic notch rather than dicrotic wave were used in the current study because the dicrotic wave was often absent in the digital pulse at baseline and frequently not clearly distinguishable during whole-body, periodic acceleration. The detection of the dicrotic notch was aided by the peak of a characteristic upward deflection wave in the second derivative of the digital pulse, whereas there were no distinguishing identifying points in the first or second derivatives of the pulse for the dicrotic wave.

The fall in dicrotic notch, which occurs with whole-body, periodic acceleration, indicates that significant concentrations of NO are produced from increased activity of eNOS that cause vasodilatation of resistance blood vessels. The current study demonstrates that the amount of NO released into the circulation is sufficient to effect a hemodynamic response. Similar falls in the dicrotic notch occur with therapeutic doses of organic nitrates.^{16,18,24,35} Dicrotic notch position changes contrast with serum nitrite levels measured after interventions designed to increase or decrease NO release. Here, infusions of nitrite in volunteers to reproduce the serum changes for this metabolite of NO fail to effect vasodilatation as measured by forearm blood flow measurements. Lauer et al³⁶ investigated the accuracy of metabolic markers of NO in humans by correlating changes in forearm blood flow after stimulation of eNOS with acetylcholine (1 to 10 μ g/min) that dose-dependently augmented venous nitrite levels by maximally 71%. This effect was paralleled by an almost fourfold increase in forearm blood flow. Intraarterial infusion of nitrite in concentrations obtained with acetylcholine had no effect on forearm blood flow. Inhibition of eNOS with N(G)-monomethyl-L-arginine; 4–12 mmol/min dose-dependently reduced basal serum nitrite and forearm blood flow by 90%. In contrast, venous nitrate and total nitrate remained unchanged during these interventions. Forearm blood flow and serum nitrite were highly correlated but not with other metabolites such as serum nitrate and total nitrite/nitrate. Therefore, serum nitrite serves as a marker of acute changes in regional eNOS activity but in concentrations that are vasodilator inactive.

The waxing and waning of the descent of the dicrotic notch during whole-body, periodic acceleration suggests that NO is released in a pulsatile manner from eNOS. This is consistent with NO electrode measurements of NO after endothelial NO stimulation.^{37–39} Tsoukias et al⁴⁰ developed a mathematical model to explain the benefits of pulsatile bursts of NO from eNOS. They noted that endothe-

lial cells produce NO, which can diffuse to smooth muscle where it activates soluble guanylate cyclase, leading to cyclic guanosine monophosphate (cGMP) formation and smooth-muscle relaxation, but the close proximity of RBCs suggests that a significant amount of NO released might be scavenged by blood. They formulated a mathematical model for NO transport in an arteriole to test the hypothesis that transient, burst-like NO production can facilitate efficient NO delivery to smooth muscle and reduce NO scavenging by blood. The model simulations predict the following: (1) the endothelium can maintain a physiologically significant amount of NO in smooth muscle despite the presence of NO scavengers such as hemoglobin and myoglobin; (2) under certain conditions, transient NO release presents a more efficient way for activating soluble guanylate cyclase and can increase cGMP formation several fold; and (3) frequency-dependent rather than amplitude-dependent control of cGMP formation is possible. Their mathematical model is consistent with pulsatile release of NO reported with the NO electrode as well as the cyclic movement of the dicrotic notch observed in the current study.

CONCLUSIONS

Passive exercise with whole-body, periodic acceleration produces an important component of the beneficial effects attendant with active exercise. Whole-body, periodic acceleration produces increased pulsatile shear stress, leading to vasodilation and a fall in the dicrotic notch, consistent with increased NO bioactivity. This is most likely due to activation of eNOS since in endothelial arterial and venous cell preparations, pulsatile shear stress increases eNOS messenger RNA expression and eNOS promoter as a direct function of the applied shear stress.⁴¹ Therefore, whole-body, periodic acceleration might substitute for or compliment active exercise in those patients whose medical condition limits physical activity.

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