# Use of simultaneous pressure and velocity measurements to estimate arterial wave speed at a single site in humans

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**Davies, Justin E., Zachary I. Whinnett, Darrel P. Francis, Keith Willson, Rodney A. Foale, Iqbal S. Malik, Alun D. Hughes, Kim H. Parker, and Jamil Mayet.** Use of simultaneous pressure and velocity measurements to estimate arterial wave speed at a single site in humans. *Am J Physiol Heart Circ Physiol* 290: H878–H885, 2006. First published August 26, 2005; doi:10.1152/ajpheart.00751.2005.—It has not been possible to measure wave speed in the human coronary artery, because the vessel is too short for the conventional two-point measurement technique used in the aorta. We present a new method derived from wave intensity analysis, which allows derivation of wave speed at a single point. We apply this method in the aorta and then use it to derive wave speed in the human coronary artery for the first time. We measured simultaneous pressure and Doppler velocity with intracoronary wires at the left main stem, left anterior descending and circumflex arteries, and aorta in 14 subjects after a normal coronary arteriogram. Then, in 10 subjects, serial measurements were made along the aorta before and after intracoronary isosorbide dinitrate. Wave speed was derived by two methods in the aorta: *1*) the two-site distance/time method (foot-to-foot delay of pressure waveforms) and *2*) a new single-point method using simultaneous pressure and velocity measurements. Coronary wave speed was derived by the single-point method. Wave speed derived by the two methods correlated well ($r = 0.72$, $P < 0.05$). Coronary wave speed correlated with aortic wave speed ($r = 0.72$, $P = 0.002$). After nitrate administration, coronary wave speed fell by 43%: from 16.4 m/s (95% confidence interval 12.6–20.1) to 9.3 m/s (95% confidence interval 6.5–12.0, $P < 0.001$). This single-point method allows determination of wave speed in the human coronary artery. Aortic wave speed is correlated to coronary wave speed. Finally, this technique detects the prompt fall in coronary artery wave speed with isosorbide dinitrate.

coronary artery hemodynamics; coronary arteries; wave intensity analysis; coronary velocity; coronary flow; interventional cardiology; pulse wave velocity

METHODS HAVE NOT BEEN AVAILABLE to measure wave speed in the human coronary artery, but wave speed measured in the aorta has repeatedly been shown to predict cardiac events (3, 17, 19). The standard approach for measuring wave speed relies on measurement of the time taken ($\delta t$) for a pressure wave to travel between two sites a known distance apart ($\delta s$). The pressure curves at the two sites may be acquired simultaneously with a pair of transducers or, alternatively, with one transducer moved between two positions with subsequent gating to the R wave of the ECG. The time delay ($\delta t$) is measured between the arrival of an identifiable point on the pressure wave, such as the "foot," and wave speed ($c$), calculated as follows: $c = \delta s/\delta t$. This method is commonly referred to as the "foot-to-foot" method. Early work was invasive, in that catheters were used to acquire simultaneous pressure waveforms in the aorta (7). Arterial waveforms are more commonly acquired using pressure transducers, Doppler ultrasound, or applanation tonometry at peripheral sites. With this approach, it is possible to derive the average wave speed noninvasively over a length of the arterial tree, most commonly the aorta, from the carotid to the femoral level.

Despite the simplicity of this method for measuring wave speed, there are several potential sources of inaccuracy. Noninvasive techniques rely on an estimation of the distance traveled between the measured points, which varies between patients, especially when arteries become more tortuous with age. The foot-to-foot method also depends critically on accurate determination of the foot of the systolic curve, which can be difficult to identify unambiguously (whether data are acquired invasively or noninvasively), a difficulty not eliminated by adoption of alternative identifiable points on the blood pressure curve, such as the ascending systolic curve (10) or the dicrotic notch (5).

The human coronary artery has eluded wave speed calculation by these methods for practical reasons: *1*) It is difficult to obtain coronary pressure waveforms noninvasively. *2*) Even invasive measurement with intracoronary pressure wires may be inadequate for velocity measurement, because the segments of coronary artery with consistent properties are not long enough for there to be a measurable time interval between recognizable points on the pressure curves at the two respective positions.

It has recently been recognized that, in certain circumstances, wave speed can be calculated from simultaneous measurements of pressure and fluid velocity at one point (8) by careful analysis of the pressure-velocity loops (12). This method uses simultaneously acquired pressure and velocity data from a single position within a vessel to ascertain the wave speed from the gradient at the linear portion of the plot at the start of systole. This technique has been validated in vitro (13) and in vivo (14) with the foot-to-foot method and has been used to determine the wave speed in the ascending aorta of patients with cardiovascular disease (11). However, this pressure-velocity loop method relies on a period during which only a single wave impulse is present (e.g., the early part of the systolic upstroke in the aorta). This restriction makes the pressure-velocity loop method unsuitable for wave speed analysis in the coronary arteries, because coronary arteries are subject to influences from the aortic and microcirculatory ends (31).

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We have developed a new technique that extends the principle of the pressure-velocity loop method and can derive wave speed ($c$) by a formula that minimizes net wave energies (*Eq. 1*) over complete cardiac cycles, where ρ is the density of blood, and dP and d$U$ are the changes in pressure and velocity, respectively, over one sampling period. The derivation of this expression for the wave speed is given in the APPENDIX.

$$c = \frac{1}{\rho}\sqrt{\frac{\sum dP^2}{\sum dU^2}} \qquad (1)$$

This single-point technique uses simultaneously acquired pressure (P) and velocity data ($U$) from a single position within a vessel. It is particularly advantageous in the coronary arteries, inasmuch as it does not require the vessel to be long enough for two measurements nor does it rely on a period during which there is only a single wave impulse.

The aims of this study were *1*) to compare the wave speeds derived using this single-point technique with those derived by the conventional foot-to-foot technique in the aorta, *2*) to use the single-point technique to derive coronary artery wave speed and compare it with central aortic wave speed, and *3*) to use the single-point technique as a method to detect acute changes in coronary wave speed resulting from the intracoronary infusion of nitrate.

## METHODS

### *Subjects*

Fourteen volunteers [56 yr (SD 11), 10 women and 4 men] were recruited from patients scheduled for coronary angiography in whom coronary artery disease was considered a relatively low probability. Exclusion criteria included previous coronary intervention, valvular pathology, regional wall motion abnormality, rhythm other than sinus, or the use of nitrates in the proceeding 24 h. The study was approved by the St. Mary's Hospital ethical committee and performed in accordance with institutional guidelines. All subjects gave written informed consent.

### *Precatheterization*

Although structural composition is considered to be the principal determinate of arterial physiology, many nonstructural physiological parameters have important regulatory roles. These may be influenced by physical (6, 15, 26), psychological (16), and pharmacological (21, 24, 28–30) factors.

*Physical factors.* To minimize the effects of physical exertion, all subjects rested in bed for 1 h before angiography. Subjects who smoked were not excluded from the study but were asked to refrain from smoking for 24 h (34, 35). Similarly, subjects were required to abstain from coffee (34) and alcohol (33) for ≥12 h before the study. Subjects were not studied within 9 h of eating.

*Psychological factors.* To minimize psychological stress, the procedure was carefully explained during the consent phase, and the subjects had ample opportunity for further clarification and reassurance.

*Pharmacological factors.* To ensure that we were studying the acute effects of nitrate, we requested that the patients try to avoid using nitrate for the 24-h period before the procedure. All other medications recommended by the patient's physician were continued, as is normal practice for coronary angiography in our institution.

### *Cardiac Catheterization*

Cardiac catheterization was undertaken via the femoral approach. After diagnostic angiography, studies were closely inspected by two operators for the presence of coronary artery disease. Only in subjects with angiographically normal coronary arteries were hemodynamic parameters recorded. Offline measurements of coronary artery diameters were made using quantitative coronary angiography (MDQM-QCA).

### *Hemodynamic Recording*

Pressure and velocity recordings from the aorta and coronary arteries were made using 0.014-inch-diameter Wavewire and Flowire (Volcano Therapeutics, formerly Jomed), respectively. An analog output from the Wavewire and Flowire consoles and ECG to a National Instruments DAQ-Card AI-16E-4 was acquired at 1 kHz using Labview. Considerable care was taken to ensure accurate alignment of pressure and velocity wires within the vessel. Once in situ, small rotational movements of the Flowire were used to obtain the peak Doppler blood velocity, and the standard cosine correction was applied in large arteries, where the wire was not constrained to lie parallel to flow. Data were subsequently analyzed using a custom software package designed with Matlab (Mathworks, Natick, MA).

### *Study Protocol*

In all subjects, after a normal coronary angiogram, a Judkins right diagnostic catheter was inserted, and pressure and flow wires were passed beyond the distal end into the aorta. Pressure and velocity were then meaured simultaneously at multiple points along the aorta starting from the aortic root. At each location, measurements were recorded for 1 min. In 10 of the patients, the wires were withdrawn by 10-cm intervals and recordings were made for 1 min at each position to enable calculation of aortic wave speed by the foot-to-foot technique. The left coronary circulation was then intubated with a Judkins left diagnostic catheter. The pressure and flow wires were passed into the proximal part of the left main stem, left anterior descending, and circumflex arteries in turn, with 1-min recordings at each location. The wires were then withdrawn into the left main stem, data acquisition was started, 1 mg of intracoronary isosorbide dinitrate was administered, and recording was continued for 1 min.

### *Derivation of Wave Speed*

The hemodynamic recordings were analyzed using customized Matlab software. The blood pressure and Doppler velocity recordings were filtered using a Savitzky-Golay filter (25) and ensembled, with the ECG used for timing. The foot-to-foot wave speed was calculated as $c = \delta s/\delta t$. The distance between the two points along the aorta ($\delta s$) had been measured physically during pullback at the time of data acquisition. The time taken ($\delta t$) was calculated by subtraction of the respective times of the onset of systolic upstroke at each point (in relation to the ECG).

The single-point wave speed was determined using *Eq. 1,* where the summations were taken over all the cardiac cycles during the measurement period (normally >50 beats). We calculated wave speed by this technique at serial locations along the aorta and in each coronary artery. In all calculations, ρ was taken to be 1,050 kg/m$^3$.

### *Reproducibility*

Reproducibility of hemodynamic recordings was excellent. The within-patient standard deviation was 4.5 mmHg for maximum systolic blood pressure, 4 mmHg for minimum blood pressure, and 0.06 m/s for peak Doppler velocity.

### *Statistical Analysis*

The statistical package Statview 5.0 (SAS Institute, Cary, NC) was used for analyses. Continuous data are described by mean (SD). Effect sizes are given as a mean and 95% confidence interval (CI) of the mean. Relations between continuous variables were examined by the Pearson product-moment correlation coefficient ($r$). Because the re-

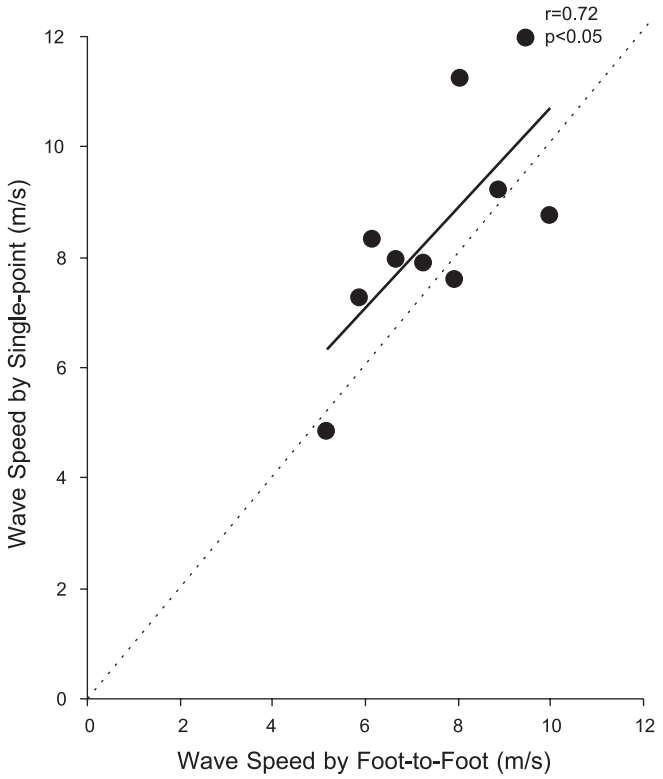


Fig. 1. Comparison of aortic wave speed derived by foot-to-foot and single-point methods. Dashed line, line of identity.

lation of wave speed to age has been described in the literature as nonlinear, we tested this relation not only with standard linear regression but also with stepwise multivariate regression with a variety of nonlinear transformations of age, namely, age, age$^2$, age$^3$, age$^4$, age$^{1/3}$, age$^{1/4}$, log(age), and exp(age$_{yr}$). Paired comparisons were made using Student's paired *t*-test. Reproducibility of hemodynamic measurements was assessed using the method of Bland and Altman. $P < 0.05$ was taken as statistically significant.

## RESULTS

Coronary artery and aortic measurements were made in all 14 subjects [56 yr (SD 11), 10 women and 4 men]. The profile for risk factors included hypertension (8), smoking (8), family history of ischemic heart disease (3), and hyperlipidemia (11). None of the subjects had diabetes mellitus. Mean systolic blood pressure was 150 mmHg (SD 22) and mean diastolic pressure was 80 mmHg (SD 11). Pharmacological therapy included aspirin (7), statins (7), calcium channel antagonists (2), and β-blockers (4). None of the subjects took nicorandil, angiotensin-converting enzyme inhibitors, or regular nitrates. Wave speed was not significantly different between subjects taking medications and those not taking medications ($P > 0.05$).

### *Wave Speed Derived From the Aorta*

Wave speed was derived from the aorta in 10 subjects using the single-point and foot-to-foot techniques. The wave speed calculated by the two methods agreed well (Fig. 1), with a correlation coefficient of 0.72 ($P < 0.05$), mean difference (single-point foot-to-foot) of 0.9 m/s, and standard deviation of the difference of 1.4 m/s.

### *Measurement of Coronary Artery Wave Speed*

In all subjects using the new single-point technique, coronary artery wave speed was derived from the left main stem, left anterior descending, and circumflex arteries. The mean coronary artery wave speed was 20.4 m/s (95% CI 17.1–23.6). Mean wave speed in individual coronary arteries was 18.8 m/s for left main stem (95% CI 15.1–22.5), 21.6 m/s (95% CI 18.1–25) for left anterior descending, and 20.8 m/s (95% CI 17.1–24.5) for circumflex (Fig. 2) arteries. Within individual patients, coronary artery wave speed was very similar in the different arteries: mean absolute difference was 3 m/s in left main stem and left anterior descending arteries, 3.2 m/s in left main stem and circumflex arteries, and 1.5 m/s in left anterior descending and circumflex arteries. The mean coronary artery diameters were 4.4 mm for left main stem, 3.7 mm for left anterior descending, and 3.2 mm for circumflex. Aortic wave speed of 7.7 m/s (95% CI 6.5–8.9) was much slower than coronary wave speed ($P < 0.001$; Fig. 2).

### *Coronary Artery and Aortic Wave Speeds*

Mean coronary artery and aortic wave speeds were correlated ($r = 0.72$, $P = 0.002$; Fig. 3). Wave speed increased similarly with age (Fig. 4) in coronary arteries ($r = 0.58$, $P = 0.02$) and aorta ($r = 0.85$, $P < 0.001$; $P = 0.16$ for difference between these two correlation coefficients).

In the literature, the relation between wave speed in the aorta and age has been described as nonlinear; therefore, we performed additional testing. By nonlinear regression analysis, the best fit was with age$^{1/2}$ for aortic wave speed ($r^2 = 0.71$) and age$^3$ for coronary wave speed ($r^2 = 0.36$). However, these curves were not appreciably different from the linear model (Fig. 4). In addition, when we tested the relation using the

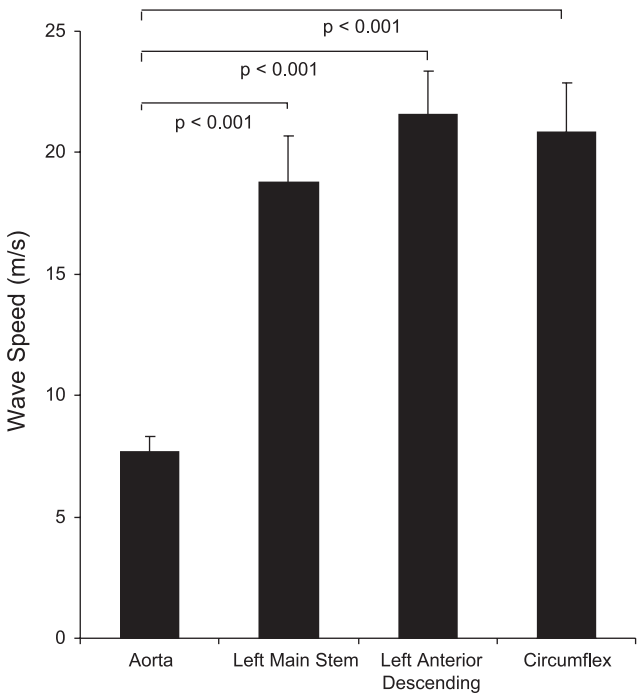


Fig. 2. Comparison of mean wave speeds in aorta with those in left main stem and left anterior descending and circumflex arteries. Mean and standard error of mean shown.

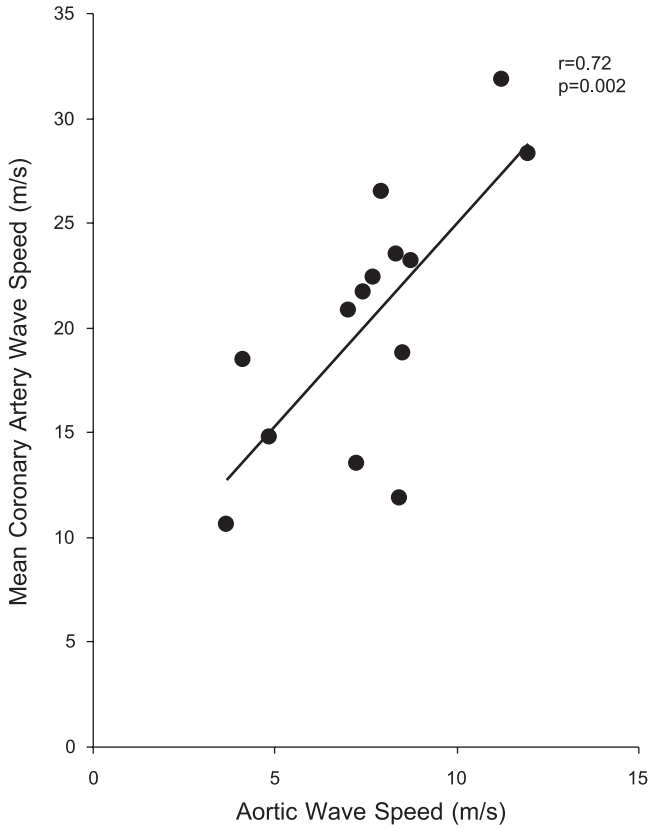


Fig. 3. Correlation between coronary artery and aortic wave speed using single-point technique.

nonparametric Spearman rank correlation test, a positive relation was confirmed between age and wave speed in the aorta ($\rho = 0.84$, $P < 0.003$) and the coronary artery ($\rho = 0.63$, $P = 0.02$).

*Effect of Isosorbide Dinitrate on Coronary Wave Speed*

After isosorbide dinitrate administration, left main stem wave speed fell by 43%, from 16.4 m/s (95% CI 12.6–20.1) to 9.3 m/s (95% CI 6.5–12.0, $P < 0.001$). Figure 5 shows individual patient wave speed data before and after isosorbide dinitrate administration. This fall in wave speed was not statistically different between subjects taking medications and those not taking medications ($P = 0.35$).

The single-point technique makes it possible to derive coronary artery wave speed beat-by-beat (Fig. 6). By this approach, we determined that a mean of 18 s was required for the coronary wave speed to reach its nadir after nitrate injection.

## DISCUSSION

We have derived arterial wave speed using simultaneous measurements of pressure and Doppler velocity at one location by a new single-point method. This method overcomes many of the limitations of other techniques and allows wave speed to be derived in small vessels. *1*) Wave speed determined by this method corresponds to conventional aortic foot-to-foot measurements. *2*) The new method is readily applicable to the coronary arteries, which have previously been difficult to study. We found a close correlation between individual subjects' aortic and coronary wave speeds. In every patient, wave speed was higher in the coronary arteries than in the aorta. *3*) The time resolution of the single-point method is sufficient for identification of acute changes, such as the rapid fall in wave speed after administration of isosorbide dinitrate.

*Single-Point Wave Speed*

Measurement of arterial wave speed has potential for use in research and as a clinical tool for assessing cardiovascular disease risk. The single-point method makes it possible to overcome many of the technical limitations of existing techniques, allowing the study of smaller and shorter vessels than has previously been possible. With use of existing techniques such as the foot-to-foot method in the coronary arteries, it is difficult to obtain sufficient temporal resolution for reliable estimates of wave speed. Alternatives such as the pressure-velocity loop, which can be used to derive wave speed in the aorta, are difficult to apply in the coronary arteries because of the presence of multiple reflected waves. We have applied the

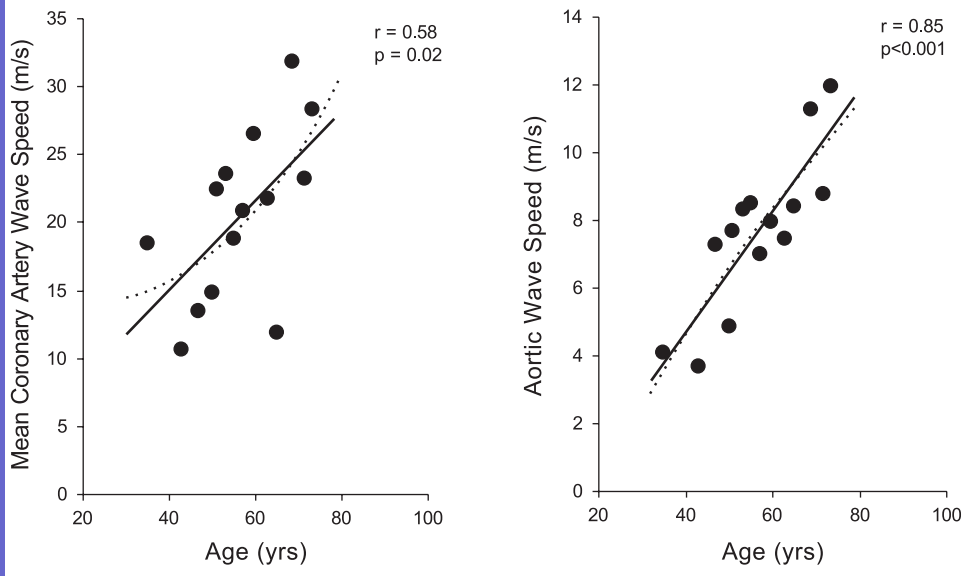


Fig. 4. Correlation between age and mean coronary artery wave speed (*left*) and aortic wave speed (*right*). Solid line, best-fit with corresponding correlation coefficient and *P* value. Dashed line, best nonlinear fit (for comparison).

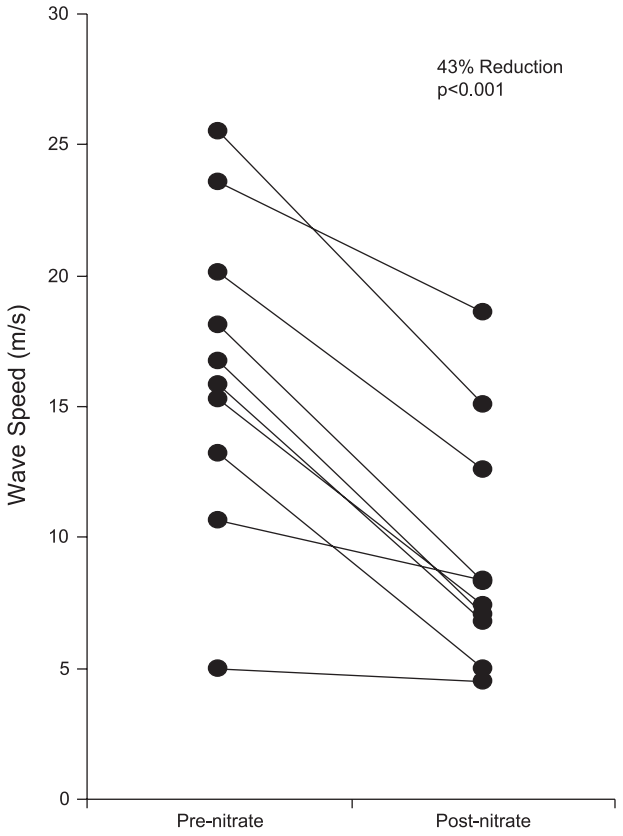


Fig. 5. Effect of isosorbide dinitrate on wave speed in left main stem coronary artery.

single-point technique to study human coronary arteries, but in principle it could be used to study wave speed in a vessel of any size, as long as simultaneous pressure and velocity can be measured. Recently, a study was presented (27) with a guide wire combining simultaneous pressure and velocity measurements. We believe that such a wire would be ideally suited for the single-point wave speed measurement.

Derivation of wave speed using the single-point technique is simple and uses equipment found in most well-equipped catheter laboratories. In contrast to other techniques that produce an average speed over a long segment of artery, this single-point technique is capable of deriving wave speed at specific points in the vascular tree. In principle, by measuring wave speed at multiple locations along an artery, this technique could be used to identify local abnormalities of wave speed, which may represent early focal disease that is manifesting as changes in arterial compliance.

Wave intensity analysis, a technique to identify and quantify individual waves, would also benefit from the single-point technique for wave speed determination. The analysis relies on the availability of the local wave speed. Until now, there has been no simple, unambiguous, automatable method for determining wave speed that can be applied to the coronary arteries and the aorta.

### *Age Dependence of Wave Speed*

Using the single-point technique, we can see that there is an increase in wave speed with age in the aorta and coronary arteries. The age dependence of aortic wave speed is well recognized (4, 20, 32), but until now it has not been possible to look for the corresponding relation in coronary arteries because of technical limitations. It is likely that the parallel increases in wave speed in the aorta and coronary arteries are manifestations of similar degenerative pathophysiological processes in both arterial beds.

### *Relation Between Wave Speeds in Coronary Arteries and Aorta*

We found a close correlation between wave speeds in the peripheral and coronary arteries that may clarify previous observations that aortic wave speed predicts not only global cardiovascular events (3, 17, 19) but also disease and events entirely within the coronary tree (9, 18, 22).

It is plausible that at-risk subjects have increased wave speed in many vascular beds. Thus the practice of measuring wave speed peripherally using noninvasive techniques may be yielding information about the global vascular state of the patient beyond the individual bed being measured.

The original work in wave speed has been performed using pulse wave techniques, which have allowed the study of large, long, and notionally uniform arteries. A newer generation of noninvasive clinical tools can measure simultaneously arterial velocity by Doppler and pressure by ultrasound vessel wall tracking (8). These may allow the pioneering work on pulse wave velocity to be built on and extended to small, relatively inaccessible, and spatially localized arterial segments. Ultimately, this may help in the study of focal and global vascular disease.

### *Relation Between Individual Subjects' Coronary Arteries*

Our findings suggest that, despite variation in the length and diameter between the coronary arteries of an individual, coronary artery wave speed is similar between an individual's coronary arteries. These similarities of wave speed measurements in vessels that are likely to differ in their pattern of distal reflection sites suggest that distal reflection is not significantly interfering with the single-point method.

### *Effect of Isosorbide Dinitrate on Wave Speed*

With use of the single-point technique, it has been possible to derive coronary artery wave speed beat-by-beat in each

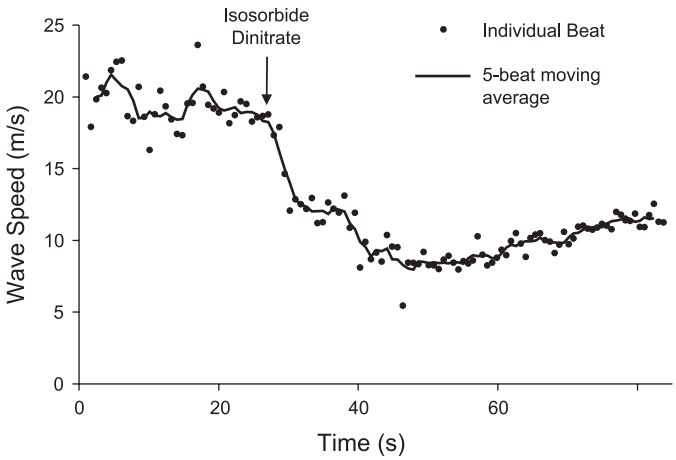


Fig. 6. Beat-by-beat coronary artery wave speed from a single subject's left main stem before and after isosorbide dinitrate.

subject. After administration of intracoronary isosorbide dinitrate, coronary wave speed is seen to fall. We believe that this represents a transient increase in vascular distensibility, in addition to the established vasodilator action of isosorbide dinitrate. These findings are consistent with studies by other groups in other vascular beds (21, 24, 28–30).

In the coronary arteries, it is not clear whether this decrease in coronary artery wave speed has a role in the antianginal mechanism of nitrates.

### *Human Coronary Wave Speed in the Context of Previous Animal Data*

On first inspection, our values of human coronary artery wave speed (averaged across the subjects of different ages) are somewhat higher than those previously reported for anesthetized horses (23) and dogs (1). However, on further consideration, there are at least two factors to take into account: *1*) The mean age of our healthy subjects was 56 yr, and age has a very large effect on wave speed in humans, as can be seen from our coronary and aortic data (Fig. 4) and aortic data from other groups (4, 32). In our younger subjects, coronary artery wave speed data were very similar to those reported in animals (1, 23). *2*) In both animal experiments (1, 23), anesthetic agents known to cause vasodilatation and reduce blood pressure were used. We now know that coronary wave speed falls dramatically with vasodilatation (at least with isosorbide dinitrate). Indeed, when we administered this vasodilator to our subjects, mean coronary artery wave speed fell by 43%, to 9.3 m/s, which is comparable to values obtained from animal experiments: 4–11 m/s in horses (23) and 8.6 m/s in dogs (1).

The wider range of ages and the absence of vasodilating general anesthesia in our study could each readily explain the higher values of wave speed in our study than in the animal studies. Nevertheless, it would be reassuring if future work could be repeated with larger numbers and include calibration of the single-point wave speed in the coronary arteries by an alternative technique.

### *Study Limitations*

Although our findings suggest that wave speed derived using the single-point technique agrees closely with the sequential foot-to-foot technique in the aorta, there are several possible explanations for the difference.

In our study, the validity of the single-point method was directly tested by reference to a conventional method only in the aorta. In the coronary artery, the only assessment was to check wave speed correlation with aortic wave speed and age and to check that an effect of nitrates is detected promptly. In the intact human, to our knowledge, no measurement of coronary artery wave speed has been published. Therefore, direct comparison of our technique against other techniques in the coronary arteries is not possible. We chose the foot-to-foot technique for comparison, because it is has been widely used for invasive measurements of wave speed in the aorta.

A second limitation of our study is that foot-to-foot measurements of wave speed were carried out from sequential (rather than simultaneous) pressure recordings. We chose this approach, because our experience was that the time from ECG to the foot of pressure wave was very reproducible, indeed, at any given measurement location; therefore, times from two locations could be subtracted to give a reliable foot-to-foot time. We believed that this small compromise, instead of the ultimate gold standard of foot-to-foot measurement using two separate catheters, is ethically preferable, because it avoids the need for a second arterial puncture that would not normally be performed for the subject's routine clinical investigation. An alternative gold standard that would avoid the need for a second arterial puncture would be a dual-pressure-sensing catheter. Such catheters would be appropriate for the aorta, but perhaps not for the coronary arteries, of these volunteer patients. To ensure that the pressure and velocity data for our single-point wave speed estimate were comparable between the aorta and coronary arteries, we wanted to use a pressure measurement system that could be safely used in both vessels. The 0.014-inch pressure wire we chose is licensed for use and is regularly used in clinical practice in the human coronary artery. For this reason, we chose to use this pressure wire and the corresponding flow wire. However, it may have been advantageous to use both approaches: the pressure and flow wires for coronary arteries and aorta plus a dual-pressure-sensing catheter in the aorta.

Comparison of methods of wave speed estimation is inherently difficult. A recent study focused in depth on the source of variation in wave speed estimates between methods in artificial laboratory models and in animals under optimized experimental conditions. Disagreements in vitro on the order of 2–3% and in animals on the order of ≥20% were found, and it was concluded that the greatest part of disagreement between wave speed estimation methods lies in random measurement error of the raw data (2).

In our study, differences between the single-point estimates of wave speed and wave speed measured by the foot-to-foot technique may represent measurement error in either technique. It might be assumed that any discrepancies between the two methods must arise from error in the single-point value (because the foot-to-foot technique is based on a simple and unimpeachable principle of distance divided by time). However, before it is assumed that all the discrepancy results from error in the single-point value, it should be remembered that the mathematical soundness of the foot-to-foot principle has to be taken in the context of technical limitations (albeit slight) of making measurements in live human volunteers. One such limitation is that although we could ensure that the distal ends of the wires were pulled by a known distance outside the body, we could not control the precise path taken by the proximal end of the catheter (inside the patient's vasculature), nor could we constrain the path of the proximal end of the wires to be identical to the path of the wave front. The aorta is curved and has a significant internal diameter; therefore, it is possible for the path traveled by the catheter during pullback to be shorter or longer than that traveled by the blood.

Although the single-point technique will work for the majority of physiological conditions, it is possible to construct theoretical models in which the single-point equation may become less accurate. One such possibility exists as a result of the difference in reflection sites between the coronary arteries and large arteries such as the aorta. Within the coronary arteries, reflection sites are considered to be more localized than those in the aorta. Theoretically, these very localized reflection sites may lead to a high correlation between forward and backward waves and possible inaccuracy in wave speed

determination. We have not been able to find such highly correlated waves, even in the human coronary circulation. Indeed, our finding of the similarity in wave speed among individual's coronary arteries, despite alteration in reflections sites, supports the use of the single-point technique in the coronary arteries.

Wave speed clearly increases with age in the aorta and coronary arteries, but it difficult to be certain from a study of this size whether the relation is linear or nonlinear. The statistical degree of fit is very similar for the linear and nonlinear models; indeed, the best-fit nonlinear models are only slightly curved. It may be that, over a wider age range or in a larger study, clearer evidence of curvature may arise. In previous studies of aortic wave speed in much larger groups of subjects, wave speed was found to increase more prominently in later life, and it is very possible that a similar age relation may exist in the coronary arteries.

Although we have found a large reduction in coronary artery wave speed after administration of nitrate, it is possible that this response may have been modulated by coadministration of other medications. No significant difference was found between wave speeds in patients taking any drug (or class of drugs) and those not taking them. However, this study was not designed to detect such differences; therefore, such differences cannot be excluded.

In conclusion, we have introduced a new technique for deriving arterial wave speed at a single point using simultaneous pressure and velocity. This technique allows wave speed to be estimated in the human coronary artery, which is difficult to assess with previous methods. Our data show that coronary wave speeds are correlated to aortic wave speeds. This helps justify studies that have measured aortic wave speed (as a surrogate for coronary wave speed) as a predictor of coronary risk. Finally, we have used beat-to-beat measurement of wave speed by the single-point method to establish that coronary artery wave speed decreases significantly after the administration of isosorbide dinitrate. This single-point wave speed calculation, in principle, could be automated and applied to simultaneous measurements of pressure and velocity obtained by any technique: if these could be obtained noninvasively, it would allow real-time study of single-point wave speed in populations.

## APPENDIX

Wave speed can be calculated from the arterial pressure-velocity relation. In the aorta, there is a segment of time in early systole when this pressure-velocity relation is linear, during which wave speed can be calculated directly by the water hammer equation: $\rho c = \Sigma dP/\Sigma dU$. In the coronary arteries, however, because reflections and multiple hemodynamic interactions alter the linearity of the pressure-velocity relation, this approach cannot be used. The wave speed information is still present but cannot be obtained from the water hammer equation. Here we present a more generally applicable formula for calculating wave speed that does not depend on the linearity of the pressure-velocity relation and yet is compatible with the water hammer equation for linear pressure-velocity relations. We present two alternative derivations for the new formula.

*Derivation 1.* We start from two observations: *1*) The use of an incorrect wave speed in the separation of the waves (31) into their forward $[dI_+ = (1/4\rho c)(dP + \rho c dU)^2]$ and backward $[dI_- = -(1/4\rho c)(dP - \rho c dU)^2]$ components introduces self-canceling forward and backward artifacts. *2*) The propagation of individual wave fronts is discrete, characterized by changes in pressure and velocity, with no summation of energy from one beat to the next.

We therefore seek the wave speed that minimizes the total forward and backward wave intensity over the cardiac cycle to reduce wave energy summation and retains periodicity.

Briefly, we define the total wave intensity as follows: $\chi = \Sigma (dI_+ - dI_-)$, where the sums are taken over the cardiac cycle.

Substituting the expressions for $dI_+$ and $dI_-$, this can be written in terms of the measured changes in pressure and velocity

$$\chi = \frac{\sum dP^2}{4\rho c} + \frac{\rho c \sum dU^2}{4}$$

The value of $\rho c$ that minimizes $\chi$ will be that which gives $d\chi/d(\rho c) = 0$; i.e.

$$\frac{-1}{4(\rho c)^2} \sum dP^2 + \frac{1}{4} \sum dU^2 = 0$$

which simplifies to

$$(\rho c)^2 = \frac{\sum dP^2}{\sum dU^2}$$

which can be applied to any segment of the arterial tree to obtain the wave speed $c$.

*Derivation 2.* An alternative approach to deriving this wave speed formula is to consider two separate components of $dU$: $dU_+ = 1/2(dU + \rho c dP)$ and $dU_- = 1/2(dU - \rho c dP)$. Their difference, $dU_+ - dU_-$ is clearly $dP/\rho c$. Therefore, the wave speed is defined by $(\rho c)^2 = \Sigma (dP)^2/\Sigma (dU_+ - dU_-)^2$. The denominator $\Sigma (dU_+ - dU_-)^2$ is a quantity that cannot directly be determined from hemodynamic measurements. However, the denominator can be approximated using the expression $\Sigma (dU_+ + dU_-)^2$, which can be readily determined, because it is equal to $\Sigma (dU)^2$, which is directly measured. For this approximation to the denominator to be valid, i.e., $\Sigma [(dU_+)^2 - 2dU_+dU_- + (dU_-)^2] \approx \Sigma [(dU_+)^2 + 2dU_+dU_- + (dU_-)^2]$, it is required that $\Sigma (dU_+dU_-)$ is small compared with $\Sigma [(dU_+)^2 + (dU_-)^2]$. We use this approximation to calculate wave speed $(\rho c)^2 \approx \Sigma dP^2/\Sigma (dU_+ + dU_-)^2 = \Sigma (dP)^2/\Sigma (dU)^2$.

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