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## Evidence of a Dominant Backward-Propagating “Suction” Wave Responsible for Diastolic Coronary Filling in Humans, Attenuated in Left Ventricular Hypertrophy

Justin E. Davies, MRCP; Zachary I. Whinnett, MRCP; Darrel P. Francis, MRCP; Charlotte H. Manisty, MRCP; Jazmin Aguado-Sierra, BE; Keith Willson, MSc; Rodney A. Foale, FRCP; Iqbal S. Malik, MRCP; Alun D. Hughes, PhD; Kim H. Parker, PhD; Jamil Mayet, FRCP

**Background**—Coronary blood flow peaks in diastole when aortic blood pressure has fallen. Current models fail to completely explain this phenomenon. We present a new approach—using wave intensity analysis—to explain this phenomenon in normal subjects and to evaluate the effects of left ventricular hypertrophy (LVH).

**Method and Results**—We measured simultaneous pressure and Doppler velocity with intracoronary wires in the left main stem, left anterior descending, and circumflex arteries of 20 subjects after a normal coronary arteriogram. Wave intensity analysis was used to identify and quantify individual pressure and velocity waves within the coronary artery circulation. A consistent pattern of 6 predominating waves was identified. Ninety-four percent of wave energy, accelerating blood forward along the coronary artery, came from 2 waves: first a pushing wave caused by left ventricular ejection—the dominant forward-traveling pushing wave; and later a suction wave caused by relief of myocardial microcirculatory compression—the dominant backward-traveling suction wave. The dominant backward-traveling suction wave ( $18.2 \pm 13.7 \times 10^3 \text{ W m}^{-2} \text{ s}^{-1}$ , 30%) was larger than the dominant forward-traveling pushing wave ( $14.3 \pm 17.6 \times 10^3 \text{ W m}^{-2} \text{ s}^{-1}$ , 22.3%,  $P = 0.001$ ) and was associated with a substantially larger increment in coronary blood flow velocity (0.51 versus 0.14 m/s,  $P < 0.001$ ). In LVH, the dominant backward-traveling suction wave percentage was significantly decreased (33.1% versus 26.9%,  $P = 0.01$ ) and inversely correlated with left ventricular septal wall thickness ( $r = -0.52$ ,  $P < 0.02$ ).

**Conclusions**—Six waves predominantly drive human coronary blood flow. Coronary flow peaks in diastole because of the dominance of a “suction” wave generated by myocardial microcirculatory decompression. This is significantly reduced in LVH. (*Circulation*. 2006;113:1768-1778.)

**Key Words:** arteries ■ blood flow ■ coronary disease ■ hypertrophy ■ microcirculation

The physical forces responsible for the coronary flow profile remain poorly understood despite intensive study. As elsewhere in the arterial circulation, ultimately it is pressure difference between the aorta and the peripheral capillaries that provides the driving force for coronary blood flow. However, unlike most other systemic vascular beds, blood flow in coronary arteries peaks in diastole rather than systole, when blood pressure in the aorta is substantially lower than the peak systolic pressure.

The effects of cardiac contraction on coronary flow was first considered by Scaramucci<sup>1</sup> in 1696, and the phasic nature of coronary blood flow and its relation to the cardiac cycle of the heart was originally described by Gregg and

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Sabiston<sup>2</sup> in 1957. Since then, the “vascular waterfall”<sup>3</sup> and “intramyocardial pump”<sup>4</sup> models have considered the importance of increasing myocardial pressure in impeding coronary blood flow. The “time-varying elastance”<sup>5</sup> model described the importance of left ventricular stiffness and contraction of fibers surrounding intramyocardial blood vessels on coronary blood flow.<sup>6</sup>

Of these, the model that is best able to incorporate the dynamics of the cardiac cycle is the intramyocardial pump,<sup>4</sup> which attributes systolic-diastolic variations in coronary flow to an active intramyocardial pump and not resistances varying

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over the cardiac cycle. Like the other experiments,<sup>1–3,5,6</sup> the experiments studying the intramyocardial pump<sup>4</sup> theory were highly invasive and suitable only for animal experiments.

We wanted to develop a technique with finer temporal resolution that would allow us to address these dynamic interactions within the cardiac cycle between proximal and distal influences on coronary flow. It was important that the technique could be readily applied to living human subjects, so that normal human physiology and human pathophysiology could be ethically studied.

The combination of new measurement technology and new analysis methodology has now made this possible. Miniaturized pressure- and flow-sensing wires suitable for use in coronary arteries of the living human are now available and approved for clinical use (Volcano Therapeutics, Inc, formerly Jomed, Inc, Rancho Cordova, Calif). Analysis of wave intensity<sup>7–9</sup> explains phasic flow in terms of a series of wavefronts that underlie the changes in pressure and flow in arteries. By quantifying these wavefronts, it is possible to determine the relative importance of aortic and microcirculatory contributions to coronary blood flow. This approach has proved valuable in understanding the patterns of flow, pressure, and wave reflection in systemic arteries<sup>7,10–13</sup> and has recently been applied to the coronary arteries of animal models.<sup>9</sup>

By applying this technique to identify the nature of the waves in human coronary arteries, we can cast light on how the complex interaction of ventricle, coronary artery, and myocardial microcirculation produce the recognizable coronary flow profile. We can also study the effect of conditions that may affect these waves. Left ventricular hypertrophy (LVH) is a classic example of such a condition, where distortion of myocardial architecture causes myocardial cell hypertrophy and fibrosis as well as intramyocardial arteriolar wall thickening and increased perivascular fibrosis.<sup>14</sup> Such structural changes lead to physiological alterations resulting in a change in the coronary blood flow profile. Although studies have demonstrated altered coronary flow reserve<sup>15</sup> and coronary vascular resistance,<sup>16</sup> neither is able to provide a mechanistic explanation for the cause of the altered flow profile.

In this study, we have applied wave intensity analysis to human coronary arteries to (1) identify and quantify the waves driving human coronary artery blood flow; (2) use direct measurement of waves of proximal (aortic) and distal origin (myocardial microcirculation) to explain why coronary flow peaks in diastole, when aortic blood pressure has already fallen; and (3) determine whether waves arising from coronary artery microcirculation are altered in LVH.

## Methods

### Subjects

Twenty volunteers (mean age, 54±10 years; 13 female) 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 preceding 24 hours. All subjects gave written informed consent in accordance with the protocol approved by the local ethics committee.

Risk factors included hypertension (n=12), smoking (n=9), family history of ischemic heart disease (n=4), and hyperlipidemia (n=13 with total cholesterol >5 mmol/L). None of the subjects had diabetes mellitus. Pharmacological therapy included aspirin (n=10), statins (n=8), calcium channel antagonists (n=2),  $\beta$ -blockers (n=5), angiotensin II blockers (n=1), ACE inhibitors (n=1), and  $\alpha$ -blockers (n=1). None of the subjects took nitrates or nicorandil.

### Before Catheterization

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, psychological, and pharmacological factors.

#### Physical Factors

To minimize the effects of physical exertion, all subjects rested in bed for 1 hour before angiography. Subjects who smoke were not excluded from the study but asked to refrain from smoking for 24 hours. Similarly, subjects were required to refrain from coffee and alcohol for at least 12 hours before study. Subjects were also not studied within 9 hours of eating.

#### Psychological Factors

To minimize psychological stress, all subjects had careful explanation of the procedure during the consent phase and ample opportunity for further clarification and reassurance.

#### Pharmacological Factors

All oral and sublingual nitrates were stopped 24 hours before the procedure.

### Cardiac Catheterization

Cardiac catheterization was undertaken through the femoral approach. After diagnostic angiography, studies were closely inspected by 2 operators for the presence of visual coronary artery disease. Only subjects with angiographically normal coronary arteries proceeded to hemodynamic recordings.

### Hemodynamic Recording

Pressure and velocity recordings from aorta and coronary arteries were made by using 0.014-inch diameter Wavewire and Flowwire (Volcano Therapeutics, Inc), respectively. Analogue output feeds were taken from the Wavewire and Flowwire consoles and ECG into a National Instruments DAQ-Card AI-16E-4 (National Instruments, Austin, Tex) and 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 were made to the Flowwire to obtain the peak Doppler blood velocity. Data were analyzed off-line, using a custom software package designed with Matlab (Mathworks, Inc, Natick, Mass).

### Study Protocol

In all subjects, after a normal coronary angiogram, the left coronary circulation was then intubated with a Judkins left diagnostic catheter. A pressure and Doppler flow wire was then passed into the proximal segment of the left main stem, left anterior descending, and circumflex artery in turn. Wires were carefully positioned to ensure that the sensor tip of each wire was aligned. Simultaneous recording of pressure and velocity was made for 1 minute at each location. Because precise alignment in time of the pressure and velocity signals is important for this analysis, we performed a series of timing calibration tests. In an in vitro preparation, we rapidly injected a small bolus of saline and measured the time delay in the raw voltage signals between the foot of the Doppler signal and the foot of the pressure waveform. A total of 62 injections were performed, and the mean delay was 5.1 ms (95% confidence interval [CI], 4.4 to 5.8 ms). To correct for the difference in processing times of the 2 signals, we therefore advanced all velocity signals in the clinical study by 5 ms.

**TABLE 1. Origin and Nature of Waves From Simultaneous Measurements of Pressure and Flow**

Pressure	Velocity	Wave Origin	Wave Nature
↗	↗	Aortic end (proximal origin)	Accelerating
↖	↗	Microcirculatory end (distal origin)	Decelerating
↘	↖	Microcirculatory end (distal origin)	Accelerating
↙	↖	Aortic end (proximal origin)	Decelerating

### Analysis of Hemodynamic Data

The recorded data were analyzed with the use of customized Matlab software. The blood pressure and Doppler velocity recordings were filtered by using a Savitzky-Golay filter<sup>17</sup> and ensembled by using the ECG for timing. Mean wave intensity was calculated from the left main stem, left anterior descending, and circumflex artery in each patient. This mean wave intensity was used in all analysis. In the present study, we have considered diastole to start with the onset of ventricular relaxation, as described by Wiggers.<sup>18</sup>

### Identifying the Origin and Nature of a Wave

Waves are responsible for directing the flow of blood in the coronary artery circulation. These waves can originate from both the upstream aortic (proximal origin) and downstream microcirculatory (distal origin) ends of the artery and can either accelerate or decelerate the flow of blood. When only pressure or velocity alone is known at a single site of measurement, it is not possible to determine the origin and nature of a wave. To identify the origin and nature of these waves, it is necessary to have simultaneous recordings of pressure and velocity.

Increases in pressure can result in either acceleration or deceleration of blood, depending on the origin of the pressure wave (Table 1). An increase in pressure originating from the aortic end (proximal origin) of the vessel will accelerate blood velocity (Figure 1A). In contrast, if the increase in pressure originates from the downstream microcirculatory end (distal origin), blood velocity will decelerate (Figure 2A). In both cases, the rise in pressure is considered by wave intensity theory to be as a result of a compression wave, which has a “pushing” effect.

The opposite pattern is found with decreasing pressure. A decrease in pressure originating from the proximal end will decelerate blood flow (Figure 2B), and a decrease originating from the distal end will accelerate flow (Figure 1B). Any decrease in pressure is considered by wave intensity theory to be a result of expansion waves, which have a “suction” effect.

### Separating Coincident Waves From Proximal and Distal Origins

The simple principles described above will identify the origin and nature of waves in most parts of the arterial circulation. However, in the coronary arteries, waves from opposite ends of the artery can occur simultaneously. To identify the origin and nature of these overlapping waves, some additional mathematical steps are required. The change in pressure is separated into wave components originating from the proximal end ( $dP_+$ ) and distal end ( $dP_-$ ), using the following formulas, where  $\rho$  is the density of blood (taken as 1050 kg m<sup>-3</sup>),  $c$  is the wave speed calculated using the single-point equation described below,<sup>19</sup>  $dP$  is the incremental change in coronary artery pressure, and  $dU$  the incremental change in blood velocity:



**Figure 1.** Acceleration of blood in the human coronary artery can occur from either (A) compression waves originating from the aortic end or (B) expansion waves originating from the microcirculatory end.



**Figure 2.** Deceleration of blood in the human coronary artery can occur from either (A) compression waves originating from the microcirculatory end or (B) expansion waves originating from the aortic end.

$$dP_+ = \frac{1}{2}(dP + \rho c dU)$$

$$dP_- = \frac{1}{2}(dP - \rho c dU)$$

The wave originating proximally is given by  $dP_+$ . Positive values indicate an accelerating wave, and negative values indicate a decelerating wave. The wave originating distally is given by  $dP_-$ , where conversely positive values indicate a decelerating wave, and negative values indicate an accelerating wave.

### Calculation of Wave Speed in the Coronary Arteries

To calculate wave intensity requires local measurement of wave speed. We have used the single-point technique, which uses simultaneous measurement of pressure and flow to determine wave speed in the following equation, where the sums are taken over an integer number of cardiac cycles.<sup>19</sup>

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

### Calculation of Coronary Artery Wave Intensity

Using wave intensity analysis, it is possible to separate and quantify the waves present in the coronary artery circulation into those originating from (1) the proximal end ( $WI_+$ ) and (2) the distal end ( $WI_-$ ) of the artery.  $WI_{net}$  represents the net wave intensity, the sum of  $WI_+$  and  $WI_-$ . We have used a convention of defining wave intensity as the product of the first time derivatives of pressure and velocity, so that the results are independent of the sampling frequency used.<sup>20</sup>

$$WI_+ = \frac{1}{4\rho c} \left( \frac{dP}{dt} + \rho c \frac{dU}{dt} \right)^2$$

$$WI_- = -\frac{1}{4\rho c} \left( \frac{dP}{dt} - \rho c \frac{dU}{dt} \right)^2$$

$$WI_{net} = WI_+ + WI_- = \left( \frac{dP}{dt} \right) \left( \frac{dU}{dt} \right)$$

### Quantification of Waves

Cumulative wave intensity was calculated for each wave by measuring the area under the curve. The proportion of cumulative wave intensity was calculated by expressing the cumulative wave intensity from an individual wave as a percentage of total cumulative wave intensity in the cardiac cycle. The contribution of each wave to coronary artery blood flow was calculated by measuring the corresponding velocity for each wave.

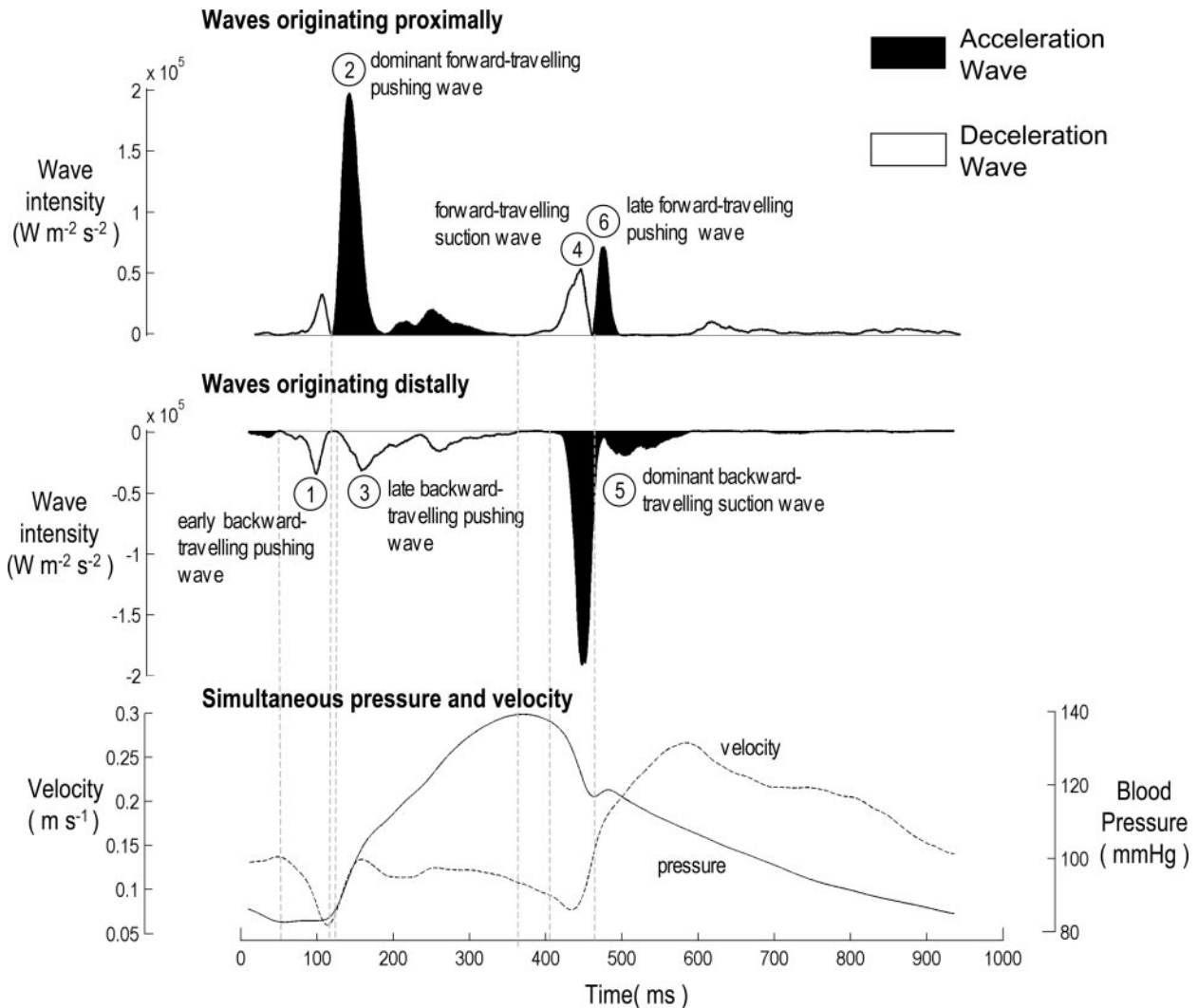
### Calculation of Wave Acceleration

Once the values of  $dP$  and  $WI$  have been calculated, the origin and nature of any given wave is known. From these values, it is possible to determine if the waves act to accelerate or decelerate the flow of blood. In each of our figures, waves responsible for the acceleration of blood are shaded (black), and those decelerating are not shaded (white).

### Statistical Analysis

The statistical package Statview 5.0 (SAS Institute Inc, Cary, NC) was used for analyses. Continuous variables are reported as





**Figure 3.** Identification of waves in the human circumflex artery, waves originating proximally ( $WI_+$ , upper panel), wave originating distally ( $WI_-$ , middle panel). Coronary artery flow velocity and pressure is shown in the lower panel. Dashed line shows the onset of each wave.

mean  $\pm$  SD at each location. Comparisons were made by using the Student *t* test. Reproducibility of hemodynamic measurements was assessed by using the Bland-Altman method. A probability value of  $<0.05$  was taken as statistically significant.

### Reproducibility

Reproducibility of hemodynamic measurements was calculated by examining, for each patient, separate 30-second recordings of blood pressure and velocity. The standard deviation of the difference, between these replicate recordings, of systolic blood pressure was 5.2 mm Hg (3% of mean value), of diastolic blood pressure was 1.9 mm Hg (2.5% of mean value), and of peak Doppler velocity was 0.057 m/s (10% of mean value).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

## Results

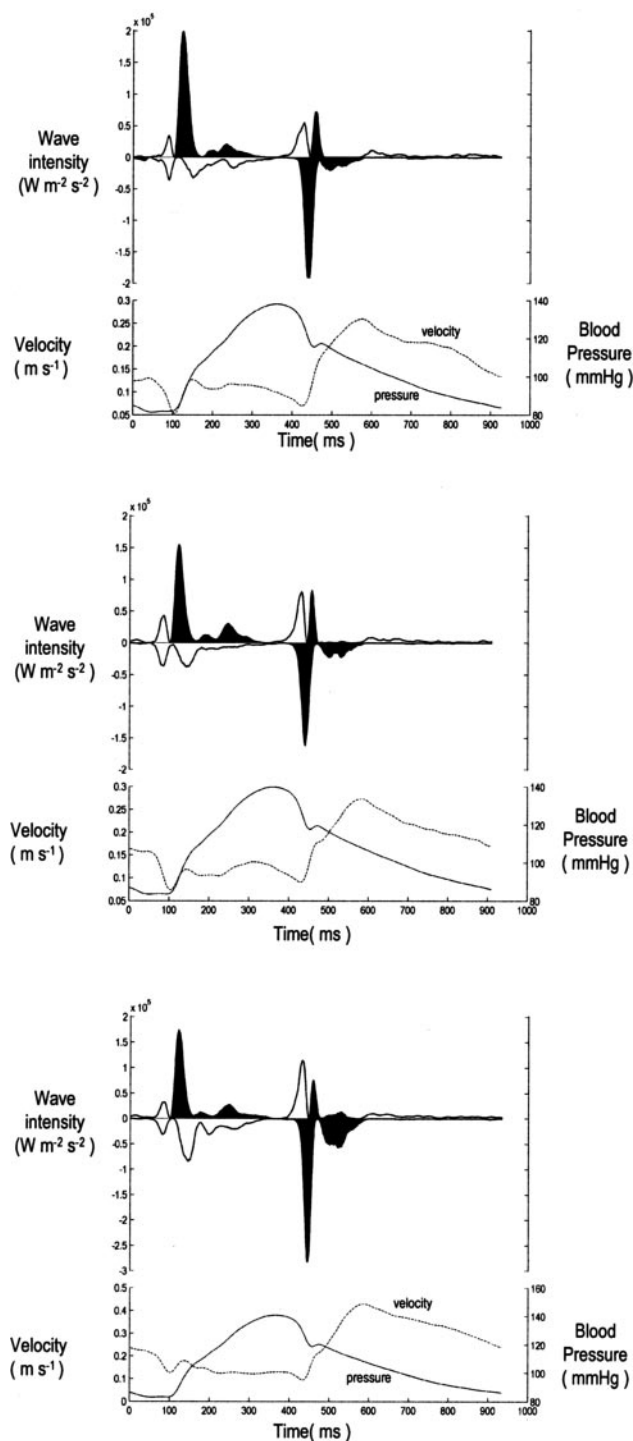
### Patient Characteristics

All subjects had good left ventricular systolic function on echocardiography. No subjects had evidence of either regional wall motion abnormalities or valvular abnormalities.

Ten subjects had LVH (septal wall thickness  $>1.2$  cm). The mean septal wall thickness was  $0.94 \pm 0.2$  cm in the non-LVH group and  $1.4 \pm 0.1$  cm in the LVH group. Mean systolic blood pressure was  $146 \pm 23$  mm Hg and mean diastolic blood pressure was  $81 \pm 13$  mm Hg. The mean blood pressure in the LVH group ( $148/82 \pm 21/9$  mm Hg) was not significantly different from the non-LVH group ( $143/80 \pm 26/16$  mm Hg). The mean coronary blood flow velocity in LVH group ( $0.43 \pm 0.52$  m/s) was not significantly different from the non-LVH group ( $0.42 \pm 0.35$  m/s,  $P = 0.95$ ).

### Consistent Sequence of Waves in the Coronary Artery

We identified 6 predominating waves in the cardiac cycle (Figure 3). These waves occur in the same sequence during each cardiac cycle. The sequence was the same in each subject, although the intensity and timing of the individual waves differed between subjects. The wave profile was very similar in each of the left coronary arteries (Figure 4). Three characteristic waves were identified during ventricular contraction, and 3 were associated with ventricular relaxation.



**Figure 4.** Identification of waves ( $WI_+$  and  $WI_-$ ) in the human circumflex artery (upper panel), left anterior descending (middle panel), and left main stem (lower panel). Pressure and velocity is shown for each recording.

Although cumulative wave intensity values varied between subjects, the proportions of individual waves were comparable between subjects. Waves were characterized by their origin and direction of travel (forward-traveling waves originating proximally and backward-traveling waves originating distally), character (pushing or suction), and effect on coronary blood flow velocity (acceleration or deceleration wave).

### Energies of Waves in the Coronary Artery

Peak wave intensity and cumulative wave intensity (area under wave intensity curve) were measured for each wave. The proportion of cumulative wave intensity (expressed as a percentage) was also calculated (Table 2). Most wave intensity (55%) occurred in association with ventricular relaxation.

The largest wave in the cardiac cycle occurred during ventricular relaxation (Figure 3, labeled ⑤), which accounted for 30% of the cumulative wave intensity. During ventricular contraction, the largest wave (Figure 3, labeled ②) accounted for only 22.3% of cumulative wave intensity. The incremental increase in coronary flow velocity was significantly larger during the ventricular relaxation ( $0.51 \pm 0.45$  m/s) than during the ventricular contraction ( $0.14 \pm 0.16$  m/s,  $P < 0.001$ ).

### Abnormal Wave Intensity in Left Ventricular Hypertrophy

In subjects with LVH, the same 6 predominant waves were identified and occurred in the same order, but the relative sizes of the waves were abnormal (Figure 5). The dominant backward-traveling suction wave decreased with increasing left ventricular septal wall thickness ( $r = -0.52$ ,  $P < 0.02$ , Figure 6). The other waves were independent of left ventricular septal wall thickness.

A strong positive correlation was found between the early-forward traveling pushing wave and the dominant backward-traveling suction wave ( $r = 0.51$ ,  $P < 0.02$ ). Subjects with LVH (septal wall thickness  $> 1.2$  cm) had only one quarter the increase in dominant backward-traveling suction wave for each unit increase in early-forward traveling pushing wave (regression slope = 0.53) when compared with non-LVH subjects (regression slope = 1.98). The early backward-traveling pushing wave was also decreased in subjects with LVH (2.8% versus 0.97%,  $P < 0.04$ ).

### Effects of Age on Waves and Coronary Wave Speed

Age has a significant effect on the cumulative wave intensity of individual waves. With increasing age, there was a progressive increase in the forward-traveling suction wave percentage ( $r = 0.64$ ,  $P < 0.002$ , Figure 7). This wave was not significantly related to wall thickness ( $r = -0.15$ ,  $P = 0.08$ ) but was related to coronary artery wave speed ( $r = 0.64$ ,  $P < 0.002$ ).

The late backward-traveling pushing wave was also found to decrease with increasing age ( $r = -0.61$ ,  $P < 0.005$ ). The other waves were not significantly affected by age. There was no association between wave intensities and any class of pharmacological therapy taken.

### Discussion

In this study, we have shown how wave intensity analysis can be used to identify and quantify the pressure-velocity waves in the human coronary artery. Second, we have found that the "suction" wave propagating backwards through the coronary tree during ventricular relaxation is the most important wave in the initiation of forward coronary blood flow. Third, this suction wave is significantly reduced in subjects with LVH.

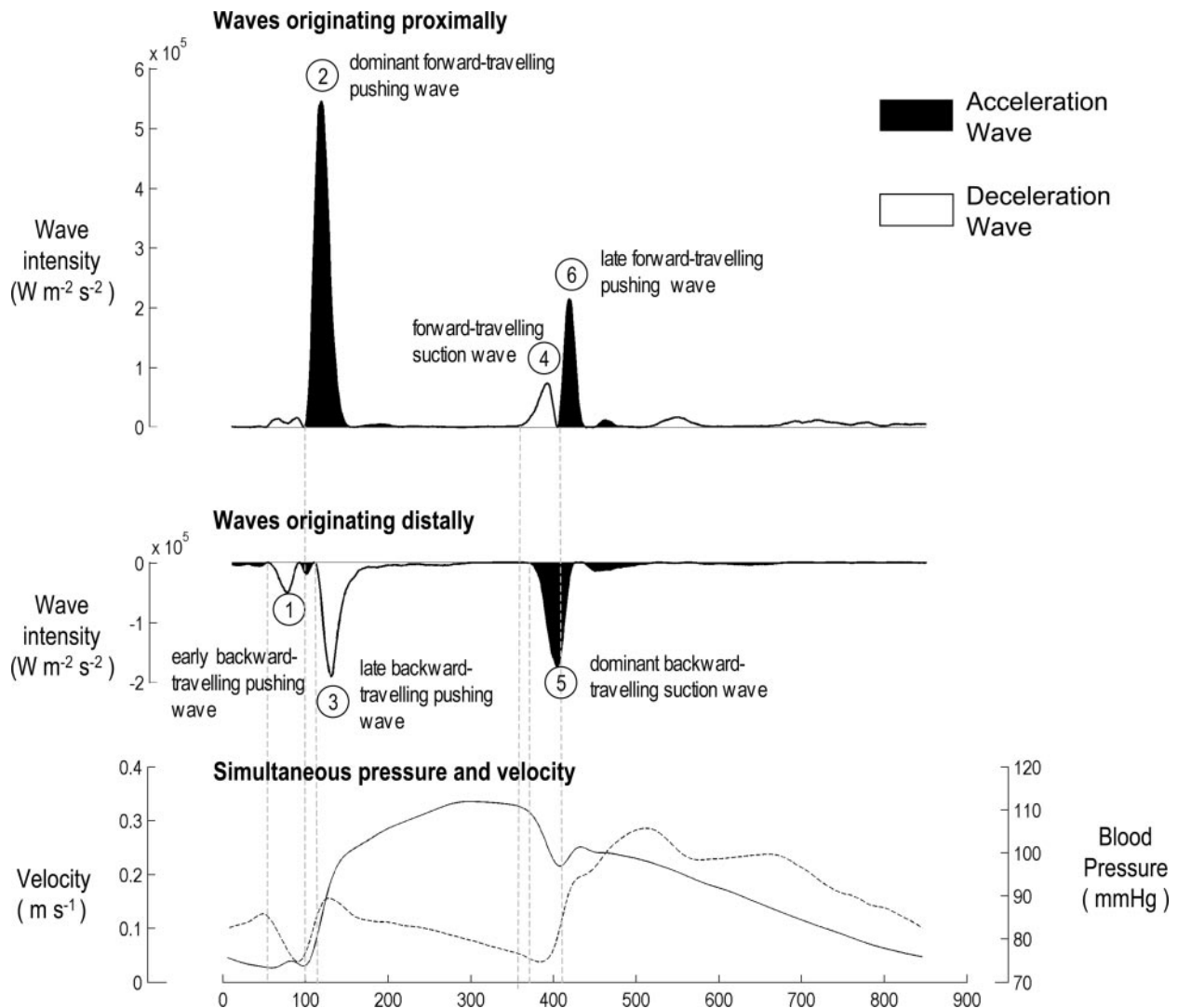
**TABLE 2. Peak Wave Intensity, Cumulative Wave Intensity, and Cumulative Wave Intensity Percentage in the Human Left Coronary Artery**

Label on Figure 3	Wave Type	Peak Wave Intensity, $\times 10^5 \text{ W m}^{-2} \text{ s}^{-2}$	Cumulative Wave Intensity, $\times 10^3 \text{ W m}^{-2} \text{ s}^{-1}$	Proportion of Cumulative Wave Intensity, %
①	Early backward-traveling pushing wave	$-0.9 \pm 1$	$1.03 \pm 1.6$	$1.9 \pm 2.1$
②	Early forward-traveling pushing wave	$6.1 \pm 19$	$14.3 \pm 17.6$	$22.3 \pm 7.9$
③	Late backward-traveling pushing wave	$-2.6 \pm 2.6$	$12.6 \pm 10.7$	$20.5 \pm 2.9$
④	Forward-traveling suction wave	$-2 \pm 1.4$	$11.2 \pm 8.7$	$18.9 \pm 4.0$
⑤	Backward-traveling suction wave	$5.5 \pm 4.6$	$18.2 \pm 13.7$	$30 \pm 5.7$
⑥	Late forward-traveling pushing wave	$2.3 \pm 2.4$	$4.0 \pm 4.0$	$6.1 \pm 2.4$

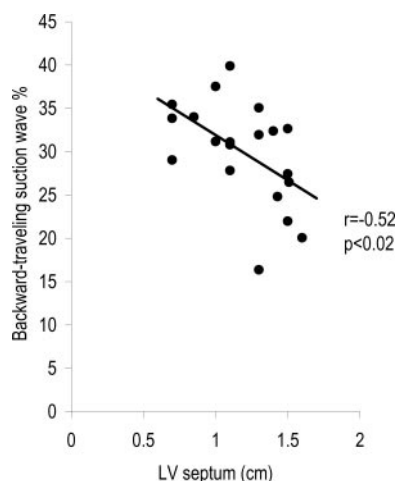
### Interpretation of the Origin of Waves in Human Coronary Arteries

Similar wave intensity patterns were identified in each subject's coronary arteries. These occur as a result of interactions between the aorta, coronary vasculature, and ventricle. Wave intensity analysis identifies the origin and direction of travel (forward-

traveling waves originating proximally and backward-traveling waves originating distally), character (pushing or suction), and effect on coronary blood flow velocity (acceleration of deceleration wave). Thus, it is possible to quantify the contribution of each wave to the development of the recognizable coronary flow profile during the cardiac cycle.



**Figure 5.** Identification of waves in the human circumflex artery of a subject with left ventricular hypertrophy (septal wall thickness, 1.6 cm), waves originating proximally ( $WI_+$ , upper panel), waves originating distally ( $WI_-$ , middle panel). Coronary artery flow velocity and pressure is shown in the lower panel.



**Figure 6.** Fall in backward-traveling suction wave percentage with increasing left ventricular septal wall thickness.

### Waves Occurring During Ventricular Contraction

The early backward-traveling pushing wave (labeled ① in Figures 3 and 8) originates from the microcirculation in early systole before opening of the aortic valve, when small vessels that permeate throughout the myocardial beds are compressed by the contracting ventricle, as described by Spaan et al<sup>4</sup> in the intramyocardial pump model. This pushing wave propagates backwards along the coronary artery toward the coronary ostium (illustrated in cartoon form in Movie I in the online Data Supplement). Because of the severe impedance mismatch between the coronary artery and the aorta, a large proportion of this wave is reflected back into the coronary artery (as a suction wave, because this is an “open-ended” reflection). This reflection is seen almost simultaneously because of the very short distance between the proximal coronary artery (where the measurements are made) and the coronary ostium. Both of these waves decelerate blood flow velocity within the coronary artery.

The dominant forward-traveling pushing wave (labeled ② in Figures 3 and 8) occurs early in systole and is caused by ventricular ejection. The wave is transmitted from the lumen of the contracting ventricle into the aorta and thence into the

coronary artery. This wave continues along the coronary artery until it meets a reflection site, such as a bifurcation or a microvascular bed, where a proportion of the wave is reflected back toward the coronary ostium, to contribute to the late backward-traveling pushing wave (labeled ③ in Figures 3 and 8, and illustrated in Movie II in the online Data Supplement). The other contributor to this wave is compression of the distal coronary microcirculation. Although both of these waves occur during ventricular contraction, the dominant forward-traveling pushing wave accelerates coronary blood flow, whereas the late backward-traveling pushing wave acts to decelerate coronary blood flow velocity.

### Waves Occurring During Ventricular Relaxation

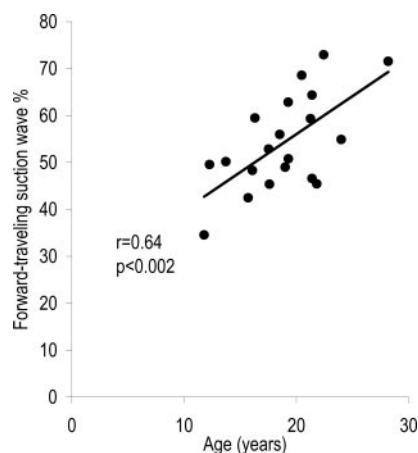
The next wave in the coronary artery circulation begins as the rate of contraction of the ventricular lumen is decreasing.<sup>21,22</sup> This deceleration results in increasing “separation” tensions within the moving column of blood in the heart and aorta. Soon these tensions build sufficiently to form a detectable wave, which is transmitted along the aorta and into the coronary artery. This forward-traveling suction wave (labeled ④ in Figures 3 and 8, and illustrated in Movie III in the online Data Supplement) has a suction action at the proximal end of the coronary artery and slows coronary artery blood flow velocity.

Continuing ventricular relaxation eases the compressive forces on the small vessels lying within the myocardium, which decreases the resistance of the microcirculation and lowers the pressure at the distal end of the coronary artery. This initiates a suction wave—the dominant backward-traveling suction wave (labeled ⑤ in Figures 3 and 8, and illustrated in Movie IV in the online Data Supplement)—causing blood to be accelerated forwards. There is a tug-of-war between these 2 competing suction waves originating from opposite ends of the artery, overlapping in time. At first, the forward-traveling suction wave predominates, but later the dominant backward-traveling suction wave becomes dominant as the myocardium ceases to compress its small vessels.

The dominant backward-traveling suction wave continues as the heart continues to relax, remaining the dominant wave until it is briefly interrupted by the late forward-traveling pushing wave (labeled ⑥ in Figures 3 and 8). This wave originates from the proximal end of the artery, coinciding with closure of the aortic valve, when aortic pressure is briefly augmented. This proximal originating wave accelerates blood still further, augmenting the actions of the distal acceleration wave in the coronary artery. This wave is short-lived, as the dominant backward-traveling suction wave once again becomes the dominant wave in the coronary artery.

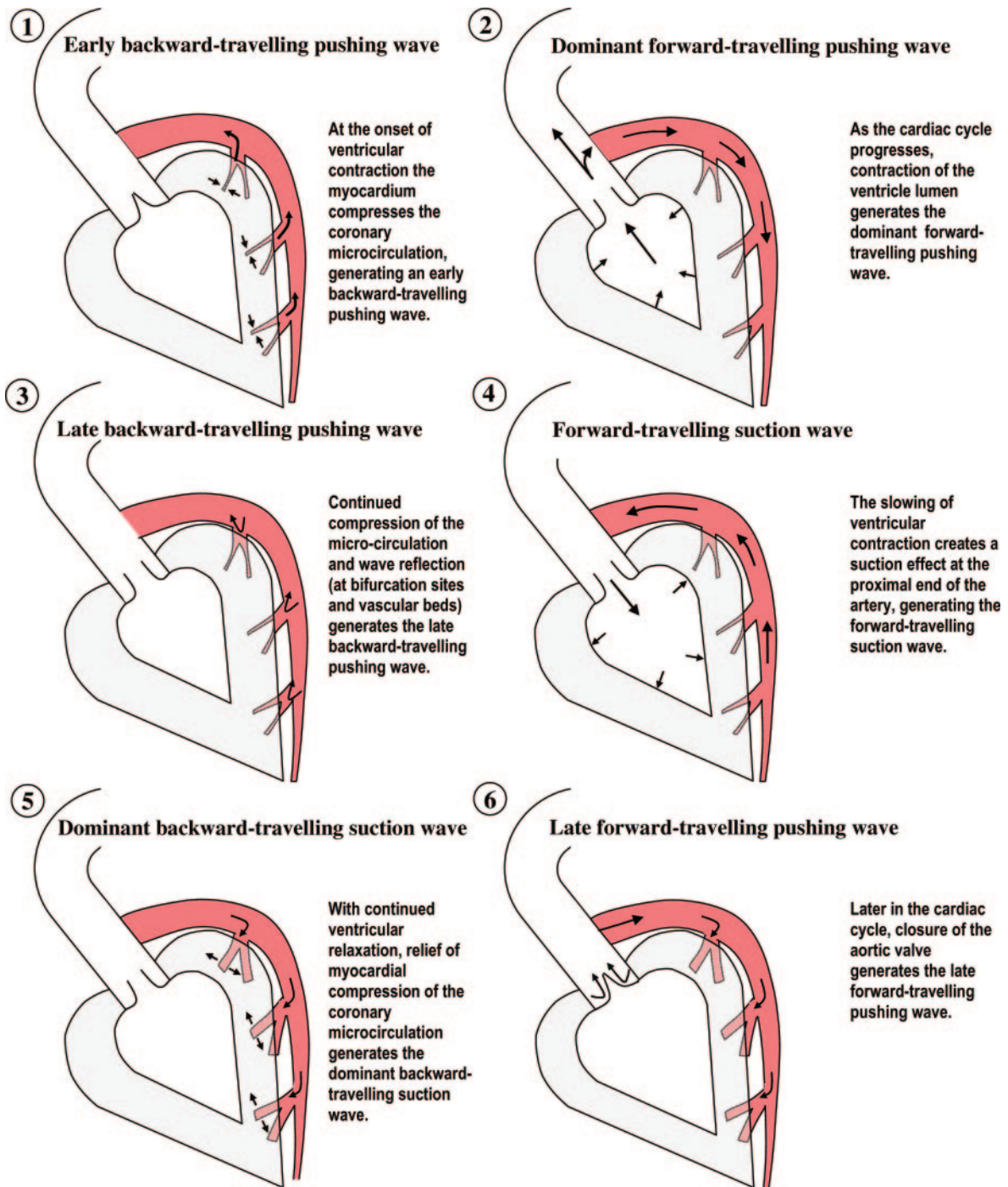
### Changes in Waves Occurring With Age

Wave speed is well recognized to increase with age in the aorta through a process of vascular degeneration, but until recently, it has not been possible to measure wave speed in human coronary arteries. We have applied a recently described technique,<sup>19</sup> using simultaneous measurements of pressure and velocity, to derive coronary artery wave speed. We have found that with increasing age the forward-traveling suction wave becomes more prominent. This may be ex-



**Figure 7.** Increase in the forward-traveling suction wave percentage with increasing age.





**Figure 8.** Sequence of energy waves in the human coronary artery during the cardiac cycle. Arrows represent direction of wave motion rather than direction of blood flow.

plained by increasing vascular stiffness (manifesting as increasing wave speed), which alters ventricular-arterial coupling, permitting a greater energy to be delivered into the coronary artery. An alternative explanation could arise from the increased blood pressure augmentation in the aorta that occurs with age. Such changes would lead to a steeper decline in pressure ( $dP/dT_{max}$ ) during ventricular relaxation and a consequent increase in the magnitude of the forward-traveling suction wave.

In the coronary circulation, such increases in the forward-traveling suction wave would be deleterious to coronary blood flow and could further enhance the tug-of-war between proximal and distal originating suction waves occurring during ventricular relaxation. This could be further exacerbated in subjects with LVH in whom the dominant backward-traveling suction wave is also reduced.

We have also found that the late backward-traveling pushing wave becomes smaller with increased age. This is the

opposite of what may be expected in other systemic arteries, in which increasing age leads to an increase in the magnitude of wave reflection. However, the coronary circulation is unique as the late backward-traveling pushing wave is not solely generated by passive reflection of the dominant forward-traveling pushing wave but also by compression of the intramyocardial vessels. These findings suggest that compression of the intramyocardial vessels may be of greater significance in the generation of the late backward-traveling pushing wave than wave reflection of the dominant forward-traveling pushing wave.

### Wave Magnitude and Blood Flow

The timing of the wave may be as important as its magnitude in determining the effects of a wave on coronary blood velocity waveform. On first inspection, the dominant forward-traveling pushing wave appears to increase coronary artery blood flow only modestly, whereas the dominant backward-traveling suction wave (which is of a similar magnitude) has a far greater effect. This paradox can be explained by considering other waves that occur at the same time in the cardiac cycle.

Let us start by considering the apparent reduction in efficacy of the dominant forward-traveling pushing wave.

The dominant forward-traveling pushing wave originates proximally as the ventricle contracts, traveling along the coronary artery and results in an increase in coronary flow velocity. This wave is large, but it is rapidly opposed by waves originating from the distal end of the vessel—the late backward-traveling pushing wave—so that blood flow forms a plateau in early systole (Figure 3, at  $\approx 140$  ms in the velocity trace). These distal-originating deceleration waves occur partly from wave reflection at bifurcation sites and the microvascular beds and also as a result of continuing compression of the microcirculatory vessels as described by the intramyocardial pump model.<sup>4</sup>

The dominant backward-traveling suction wave occurs as the ventricle continues to relax and myocardial compression of small vessels wane. This wave has several advantages, allowing it to exert a large effect on coronary blood flow velocity in comparison to the dominant forward-traveling pushing wave. First, the accelerating influence of this wave is not opposed by its own reflections, because it is directed toward an open end at the coronary ostium. Second, its opposition (arising from suction generated by relaxation of the ventricular lumen) is much shorter-lived and therefore relatively ineffectual in preventing a surge in flow. The surge created by the dominant backward-traveling suction wave is a well-recognized characteristic of coronary blood flow profiles.

Thus, using magnitude and timings of these waves, it has been possible to determine how the aorta, coronary artery, and ventricle interact to produce the characteristic coronary flow profile. Application of this analytical technique may make it possible to explain mechanisms by which pathological processes such as LVH, lead to alterations in coronary blood flow.

### Left Ventricular Hypertrophy and Wave Intensity

Subjects with LVH have the same 6 predominant waves as normal subjects, but the distribution of energies is significantly altered. The most striking differences in subjects with LVH are (1) the dominant backward-traveling suction wave percentage is decreased; and (2) the ratio between the dominant forward-traveling pushing wave and the dominant backward-traveling suction waves are significantly depressed.

Rather than considering each of these results in isolation, more insight can be gained by observing how these 2 waves affect each another. For any given increase in the dominant forward-traveling pushing wave, subjects with LVH had only one quarter the increase in dominant backward-traveling suction wave that was seen in the subjects without LVH.

This is consistent with the suction wave arising from energy originally stored in the myocardium by ventricular systole and consistent with severe disruption of this process in patients with LVH.

We speculate that in subjects with LVH, when diastole becomes shortened such as occurs in exercise, the already severely attenuated dominant backward-traveling suction wave may become critically impaired. Such a mechanism, afflicting the single wave responsible for the largest increase in coronary blood flow, may help explain why some subjects with LVH and angiographically normal coronary arteries have a reduction in coronary flow reserve<sup>15,16</sup> and have exertional angina.

### Added Value From Arterial Wave Intensity Analysis

Measurements of coronary flow reserve<sup>23</sup> by previous investigators have yielded extensive experience of coronary flow velocity in healthy subjects and identified key differences in disease states, especially coronary stenosis.<sup>15</sup> The coronary flow profile is the effect and not the cause of the underlying waves, however. If the coronary system had only one possible site of origin of waves, the blood flow profile could be fully informative. Yet, in reality, coronary waves originate from both ends of the tree, and therefore the flow profile alone cannot identify the relative contributions of the aorta, coronary artery, and intramyocardial vessels.

Investigators studying abnormalities such as LVH have realized that measuring blood flow alone cannot measure the effects of coronary microcirculatory disease directly. This has led to the use of vasodilating drugs to expose abnormalities in the coronary microcirculation by preferentially reducing microcirculatory resistance, thus indirectly measuring a consequence of the dominant backward-traveling suction wave. Wave intensity analysis allows this wave to be measured directly.

Wave intensity analysis could also be applied to study other disease processes such as coronary stenosis, microcirculatory disease, or abnormalities of ventricular function. It may even help resolve contention over mechanistic explanations, for example in the no-reflow phenomenon.

### Study Limitations

The present study offers a new technique for assessment of the waves responsible for coronary artery blood flow. To our

knowledge, this is the first publication to use this technique in human coronary arteries. Although we have made every effort to attain a “normal” population within the framework outlined by our ethical committee, there are several possible sources of limitation.

Our patient group had a wide age range (35 to 75 years). The aging process is known to alter hemodynamics in the aorta and therefore is likely to have corresponding effects in the coronary arteries. However, in our study, neither LVH nor dominant backward-traveling suction wave were significantly correlated with age, and therefore it is unlikely that the relation we have found was a result of confounding by age.

All subjects were recruited from patients scheduled for coronary angiography for investigation of ischemic heart disease. As a result, each subject was on pharmacological therapies to minimize cardiovascular risk, as prescribed by their own clinicians. Precise therapies varied between patients, with some subjects taking a single antianginal agent and others taking 3 or more. Although it is conceivable that differences in pharmacological therapies may have influenced wave energies, no statistically significant relation was identified between the number of antianginal agents and the wave energies, nor between the presence of any individual class of antianginal agent and wave energies.

We cannot be certain that the coronary arteries were normal. Subjects only underwent these hemodynamic recordings if the coronary angiogram was considered by 2 operators to be free from visible stenosis. It is possible that some subjects may have had atherosclerosis not causing stenosis. Nonstenotic disease, however, would not be expected to obstruct the propagation of waves.

Calculation of wave intensity analysis requires calculating the product of the measured changes in pressure and velocity. This can result in small variations in hemodynamics leading to large variations in the magnitude of wave energies. Although inpatient variation is usually small, interpatient variation is often large. To facilitate interpatient comparison, in addition to calculating peak wave intensity and cumulative wave intensity, we additionally calculated the proportion of cumulative wave intensity for each wave expressed as a percentage of the total cumulative wave intensity.

We have used the single-point technique in our derivation of wave speed.<sup>19</sup> This technique determines wave speed locally rather than considering a long section of artery. Although this provides an accurate estimate of wave speed, there is a theoretical risk that at very proximal reflection sites, wave cancelling may produce higher estimates of wave speed than may otherwise be expected. All of the hemodynamic measurements described in this manuscript are recorded at very proximal coronary artery sites, thereby reducing this theoretical risk to a minimum. Currently, there is no other independent and safe method for the derivation of coronary artery wave speed in humans.

The single-point technique provides a single estimate of wave speed throughout the cardiac cycle. It is possible that wave speed varies during the cardiac cycle and that our use of a single wave speed across the whole cardiac cycle may mean the calculated wave intensity profiles are not accurate. However, there is no technique currently available to measure

variations in wave speed within the cardiac cycle. To estimate the sensitivity of our analysis to variations in wave speed, we established first that the separated wave intensity ( $WI_+$  and  $WI_-$ ) profiles agreed with the net wave intensity trace ( $WI_{net}$ , whose calculation does not depend on a wave speed estimate). Second, we performed recalculations of the separated wave intensity profiles with wave speed 30% faster or slower than the central estimate. Despite this considerable range in estimated wave speed used for calculation, the same separated waves are present in each case, and the peaks are quite similar in magnitude. Our conclusion from this is that even if wave speed varied during the cardiac cycle to this degree, the separated wave intensity calculations are reasonably secure.

In our interpretation of the origin of waves in the coronary circulation, we have outlined the mechanisms most likely to generate the coronary artery wave intensity profile. Although such mechanisms provide adequate explanation, it is possible that alternative or additional interpretations may exist.<sup>24</sup>

Our study is cross-sectional and therefore cannot give data on the development or regression of LVH and its consequences on wave intensity. Therefore, our implicit assumption that LVH is the cause of the abnormalities seen in the subjects with LVH is always subject to challenge. However, we have looked extensively for potential confounders and have found no evidence that anything other than LVH itself is the causative mechanism.

## Conclusions

Six waves predominantly drive human coronary blood flow. These waves are directly and unambiguously identified by using wave intensity analysis. Peak coronary blood flow occurs in diastole because of the dominance of a “suction” wave, the dominant backward-traveling suction wave, generated by myocardial microcirculatory decompression. LVH significantly alters the distribution of these waves, markedly reducing the dominant backward-traveling suction wave.

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## Disclosures

None.

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### CLINICAL PERSPECTIVE

Coronary blood flow profile is unique, generated by interactions between the coronary arteries, cardiac myocardium, and aorta. These vascular beds influence coronary blood flow through a series of waves. We present a new technique, wave intensity analysis, which enables the magnitude, direction, and effect of each of these waves to be measured directly. By using this technique, we have identified a series of 6 predominating waves that are responsible for coronary blood flow. Waves are classified according to their origin (either aortic or coronary microcirculation) and nature (either pushing or sucking). The majority of coronary blood flow occurs in diastole as a suction wave generated by the relaxing coronary microcirculation accelerates blood flow. This wave sucks blood into the coronary microcirculation. In subjects with left ventricular hypertrophy, this suction wave was significantly decreased (33.1% versus 26.9%,  $P=0.01$ ) and inversely correlated with left ventricular septal wall thickness ( $r=-0.52$ ,  $P<0.02$ ). These differences illustrate how wave intensity analysis can be used to identify differences in the waves responsible for coronary blood flow. This may be a sensitive tool for investigation of cardiac disease pathology.