Measurements of Coronary Velocity and Reactive Hyperemia in the Coronary Circulation of Humans

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SUMMARY An acceptable method for measuring phasic coronary velocity and reactive hyperemia in humans has not been available. We have developed a doppler probe which can be coupled to surface coronary vessels at the time of cardiac surgery with a small suction cup. Phasic coronary velocity can be measured with a signal to noise ratio that exceeds 20:1. Animal studies have shown that the probe does not alter myocardial perfusion or cause tissue damage. In addition, changes in mean coronary velocity are closely related \((r = 0.97)\) to changes in coronary flow over a wide range \((15-400 \text{ ml/min})\). The characteristics of reactive hyperemia in the coronary circulation of dogs determined with the doppler system are similar to those obtained simultaneously with an electromagnetic flow meter. Transient occlusions of branch coronary vessels in patients with normal coronary arteries are not associated with significant changes in heart rate, left atrial, or mean arterial pressure. The characteristics of reactive hyperemia in normal vessels of 13 patients were as follows: although reactive hyperemia responses were demonstrable following 1 to 2-second coronary occlusions, maximal responses usually occurred with 20-second coronary occlusions; following 20 seconds of coronary occlusion, the ratio of peak to resting velocity was \(5.8 \pm 0.6\) (mean \(\pm SE\)); the ratio of repayment to debt area was \(3.1 \pm 0.2\), and the duration of the reactive hyperemia response was \(20.8 \pm 0.3\) seconds. These studies provide the first quantitative measurements of coronary reactive hyperemia in humans. Circ Res 49: 877-891, 1981

Although mean flow to the left ventricle can be assessed in patients with several techniques (Berne and Rubio, 1979; Klocke and Wittenberg, 1972), measurements of phasic coronary flow and reactive hyperemia in humans have been hampered by methodological problems.

Three methods of measuring phasic coronary flow or velocity in humans have been described. Folts et al. (1979) measured phasic coronary flow by placing an electromagnetic flow meter around the proximal right coronary artery at cardiac surgery. Because this method requires surgical dissection of the coronary vessel, it has been employed infrequently. Cole and Hartley (1977) measured phasic coronary velocity with a doppler crystal mounted at the end of a catheter which could be placed in the left or right main coronary artery. This technique has not been widely used because velocity cannot be measured in branches of the coronary tree, a large bore catheter is needed, and the stimulus used to induce ischemia (injections of contrast media) is difficult to apply quantitatively. Finally, electromagnetic flowmeters have been placed on coronary bypass grafts during cardiac surgery (Matthews et al., 1971; Bittar et al., 1972; Greenfield et al., 1972; Larsen et al., 1976; Olinger et al., 1976; Oldham et al., 1978; Oldham et al., 1979). The main problems with this approach are the flow cannot be measured in the native coronary circulation and measurements must be obtained following cardiopulmonary bypass—a procedure which may alter coronary reactivity.

We have developed a safe and easy method for measuring phasic coronary velocity and reactive hyperemia in patients at the time of cardiac surgery. Phasic velocity and reactive hyperemia can be measured in several surface coronary vessels. This paper describes experiments concerning the safety and validity of this method and the characteristics of phasic coronary velocity and reactive hyperemia in normal human vessels.

Methods

Description of the Doppler Probe

Figure 1 shows the essential features of the ultrasonic transducer. The 20-mHz crystal is piezoelectric material (P2T-5A Valtec, Hopkinton) compressional, fine-ground with gold plate on both sides, furnished from the supplier as a 1-mm diameter disc. Under the microscope, a scratch is made through the gold plating on one side of the disc and
electrical separation is checked with an ohmmeter. This forms two electrodes on the same side, and a lead is attached to each one. The leads are soldered at a 45° angle to the plane of the crystal with 50-50 tin-lead solder and a pulse dot soldering system (Circon).

The leads are 30 cm long, 38-gauge stainless steel wire (catalog no. AS633, Cooner Sales Co.). The leads are tinned before soldering to the crystal with an acid stainless steel flux (All-State Duz-All Chemtron Corp.) and 50-50 solder. The acid flux is thoroughly washed off immediately after the tinning is completed. A drop of biocompatible epoxy (no. 795 medical grade resin and no. 796 hardener, Hysol Corp.) is used to secure the soldered connections. A hemispherical lens is also formed at this time by placing a drop of epoxy on the side of the crystal opposite the lead and allowing surface tension to shape the lens. The epoxy is set in about 10 minutes by placing the crystal 4 cm from a 100-W bulb.

The silicone suction cup is cast in a lucite mold with two-part medical grade elastomer (MDX 4-4210 with catalyst, Dow Corning). Curing is accomplished with an hour exposure 5 cm from a 100-W bulb. The cup is 27 mm in diameter, 1.25 mm thick at the apex tapering to zero thickness at the circumference. The maximum depth of the cup is 3 mm. The crystal is mounted through a hole in the center of the cup such that it faces away from and lines up with vacuum and electrical lines. With the leads normal to the cup surface, the crystal is at 45° with respect to the surface of the myocardium. The leads

**FIGURE 1** The top panel is a photograph of the doppler probe, and the diagram in the bottom panel shows the essential features of the probe's design.
and vacuum line leave the cup approximately tangent to it at the apex. They are cemented in place with a single part silicone sealant (890 Medical Adhesive Silicone type A, Dow Corning). The vacuum line enters the underneath side of the cup at a point 2 mm behind the crystal. A standard luer needle hub on the vacuum line allows quick connection in the operating room. The leads are terminated in a micro plug (Switch Craft, no. 850). The weight of the assembly is about 5 g.

Description of the Doppler Meter

The doppler meter is a modification of a circuit developed by Hartley (1974, 1978). Figure 2 shows a block diagram of our system. The meter functions in the following manner. A 20-MHz carrier frequency is provided by a crystal-controlled oscillator. A digital integrated circuit divides this basic frequency by 320 to produce a pulse repetition frequency of 62.5 kHz. A gate of 0.8 µsec duration passes 16 cycles of 20 MHz to the transmitter which amplifies the signal and couples it to the transducer. Energy returning to the transmitter is detected and amplified by a receiver and passed to a dual-phase detector. There, two reference signals, locked to the transmitted frequency and separated in phase by 90°, are compared to the returning signal. During each 16-µsec receiver cycle, the phase difference between the received and transmitted signals is converted to a voltage. The time during each received cycle at which this voltage is sampled is variable. By adjusting the range control, the operator can move the sample window over a distance of 1-10 mm from the crystal face. In practice, the range control usually is adjusted so as to receive a maximal signal. Directional information is obtained by comparing the relative phase of the two outputs of the dual-phase detectors. In order to process signals containing high velocities, however, the directional circuits are automatically disabled at instantaneous frequency shifts which exceed 4 kHz. Sample and hold circuits are used to extract the doppler audio signals from the phase detector outputs. The signals are then filtered to remove the pulse repetition frequency component. Thereafter, these audio signals are passed to a dual-polarity frequency to voltage converter that is phase sensitive. The output of the converter, a voltage corresponding to instantaneous velocity, can be displayed on a strip chart recorder. The audio signal is also amplified and fed to a speaker. The speaker output is used to position the probe.

In order to improve the performance of this device, we have made several modifications of the original design. Faraday shields have been installed on the receiver input transformer to reject noise generated from external sources. Also, a solid state polarity switch is used to improve the rejection of internally generated noise. Furthermore, the sample and hold circuit has been changed to a mostly monolithic, high-speed design. This modification increases the sensitivity of the device by reducing the turn-off time of the electronic switch in the sample and hold circuit. Finally, the system's response to very high frequency shifts has been improved by the addition of a voltage-controlled,
high-pass filter. The cut-off frequency of the filter increases as peak detected velocities increases. This improves the response of the zero crossing detectors to large frequency shifts.

In Vitro Studies

To determine the maximum velocity detectable with our system, the following in vitro experiments were done. A doppler crystal was placed at a 45° angle to the long axis of the lumen of a stainless steel tube 2.5 mm in diameter. The tube was connected to a roller pump, and flow (range 15-300 ml/min) was assessed by timed-volume collection. The fluid used was saline containing 15 μm non-radioactive microspheres or blood. At multiple flow rates, measurements of velocity and timed-volume collection were performed. The doppler system can accurately measure velocities up to about 100 cm/sec (Fig. 3). Dilution of the blood 2- or 3-fold with saline did not shift the relationship between flow and velocity.

Studies in Dogs

Acute

Thirteen mongrel dogs (17-29 kg) were anesthetized with pentobarbital sodium (30 mg/kg, iv) and mechanically ventilated by an endotracheal tube with air. Oxygen and iv bicarbonate were administered to maintain blood gases and pH within the physiological range. A right thoracotomy was performed and a cannula 4 mm in diameter was placed in the proximal coronary sinus via the right atrial appendage and secured with 000 silk. Blood from the cannula could be collected in a graduated cylinder or returned to the jugular vein. Catheters were placed in both femoral arteries (for withdrawal of reference arterial samples), the brachial artery (for measurement of arterial pressure), and both femoral veins (for drug infusion).

Chronic

Chronic studies were done to determine whether the doppler probes produced any tissue damage. Three mongrel dogs (16-28 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv) and mechanically ventilated via an endotracheal tube with a mixture of air and O₂. A left thoracotomy was performed under sterile conditions and 3-5 doppler probes were placed on coronary vessels. We noted the location of the probes, removed the devices and closed the thoracotomy.

Measurement of Coronary Blood Flow with Microspheres

Microspheres 15 μm in diameter labeled with ⁸⁷Sr, ⁴⁶Sc, and ⁹⁵Nb were used in these studies. We have previously described our protocol for microsphere injection (Marcus et al., 1975). Briefly, we injected 0.7 to 3 × 10⁶ spheres of each label suspended in 0.2-3 ml of 10% dextran into the left atrium for each measurement. Prior to injection of spheres, the vial containing the microspheres and one drop of Tween-80 was agitated vigorously for 4 minutes. Microscopic examination of the spheres prepared in this manner showed that 98% of the spheres were dispersed. Occasionally, small groups of 3-5 spheres were observed. Starting 1 minute before injection and continuing until 3 minutes after injection, blood was withdrawn simultaneously from two reference arteries at a rate of 2.06 ml/min into glass syringes with Harvard pumps. The microspheres were injected slowly over a 30-second period, and the cannula was flushed over a 60-second period with 5 ml of saline. In all of the studies, we obtained two arterial reference samples.

Following the study, the animals were killed with an injection of potassium chloride, and the heart was removed. Selected transmural segments of myocardium (0.5-3.0 g) were removed, weighed, placed in glass tubes and counted for 5 minutes in a well-type γ counter. The reference blood samples were
divided into aliquots so that their counting geometry was similar to that of the issue samples. The energy windows utilized were $^{40}\text{Sc}$ 700–1500 KeV, $^{95}\text{Nb}$ 600–700 keV, and $^{85}\text{Sr}$ 400–600 keV. The isotope separation was performed using standard techniques (Rudolph and Heyman, 1967).

The blood flow was calculated using the formula:

$$BF = C_b \times 100 \times RBF - C_r$$

where $BF$ = blood flow in ml/min x 100 g, $C_b$ = counts per gram of heart, $RBF$ = reference blood flow in ml/min (rate of withdrawal from the reference arteries), and $C_r$ = total counts in the reference blood sample. The counts in the two reference blood samples were averaged.

The blood flow, sample weight, and anatomic site of each segment were punched on computer tape. Subsequent analysis was performed with a PDP/11 computer. Regional blood flows reported are the weighted mean flow of all tissue samples of a given anatomic region.

**Animal Studies**

Five types of animal studies were performed. A dog was usually used in only one of the protocols.

To assess the possibility that the electrical energy used to excite the crystal could induce cardiac arrhythmias, the wires that are usually connected to the doppler crystal were attached directly to the myocardium and excited maximally for 3 minutes in two dogs. No changes in rhythm occurred. Measurements of leakage current from the doppler meter and the recording machine did not exceed 50 $\mu$A.

To ascertain if the doppler probes could cause tissue damage, we examined the myocardium and the coronary vessels below the probes histologically. In each dog, 3–5 doppler probes were placed on coronary vessels for 2–4 hours with maximum suction (4 mm Hg), and their position was noted. In three experiments, the dogs were killed with potassium chloride, and transmural segments of myocardium were obtained from immediately beneath the probes. These samples were used to assess acute hemorrhagic damage induced by the probe. In three experiments, the thoracotomy was closed. Two days later, the dogs were anesthetized and killed, and transmural myocardial samples from below the probe sites were obtained. These samples were used to determine whether the probe induced necrosis in either the coronary vessel or the myocardium.

The selected segments of cardiac tissue and overlying epicardial vessels were fixed in formalin, stained with hematoxylin-eosin, and examined with light microscopy.

Cardiac tissue obtained from sites below 23 doppler probes did not show tissue damage that could be detected by light microscopy. In one biopsy, there was a hemorrhagic area in the epicardium that extended 50 $\mu$m into the myocardium. However, the myocardial cells and the coronary vessel appeared normal.

To evaluate the possibility that the doppler probe altered regional coronary blood flow, we measured myocardial perfusion with labeled microspheres immediately below probes placed on the dog’s left ventricle. Experiments in four dogs indicated that perfusion in the region of the myocardium just beneath the suction cup was not impaired during control conditions or during intense coronary vasodilation induced with iv adenosine (4.7 $\mu$M/kg per min) (Fig. 4). Other studies demonstrated that perfusion of the myocardium distal to the probe was also normal.

To determine the relationship between changes in mean velocity measured with the doppler and coronary flow measured by timed-venous collection, in seven dogs we measured both simultaneously over a wide range of flows. Changes in flow were induced by infusion of norepinephrine (10–40 $\mu$g/min, iv), adenosine (1.0–4.7 $\mu$M/kg per min, iv), dipyridamole (0.05–0.5 mg/kg per min, iv), and isoproterenol (2–10 $\mu$g/min, iv). We also altered coronary flow by ventricular pacing (heart rate 150–250) and hemorrhagic hypotension (decreases in mean arterial pressure from 100 to 30 mm Hg). In many experiments, we used combinations of these interventions. Prior to obtaining each measurement, flow was stable for 1–3 minutes.

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We also compared changes in coronary velocity with changes in coronary flow measured with an electromagnetic flow probe. Coronary flow was varied by partial coronary obstruction and by performing transient coronary occlusions of variable duration. The output of the two probes was compared at two points in time following the release of each occlusion: 0.25 and 2 times the duration of the occlusion.

We compared the characteristics of coronary reactive hyperemia as assessed with the electromagnetic flowmeter and the doppler velocity probe. Multiple coronary occlusions of variable duration (1-45 sec) were performed in four dogs, and responses were measured simultaneously with both devices. We examined 10-30 responses in each dog. The occlusions were separated by 1- to 3-minute intervals. The characteristics of the reactive hyperemia curves that we assessed were: the ratio of peak to resting velocity or peak to resting flow, the ratio of repayment to debt area, and the duration of the occlusion and the response (Freeman, 1935) (see Fig. 5).

**Studies in Patients**

These studies were approved by the Human Subjects Committee at the University of Iowa and performed in accordance with the Committee's recommendations. All patients involved in the study were having elective cardiac surgery. They were premedicated and anesthetized with a variety of drugs as indicated clinically (Table 1). A cannula was placed in the radial artery, and arterial pressure and the electrocardiogram were monitored continuously. A mid-ternal thoracotomy was performed, the pericardium was incised, and the heart was supported in a pericardial cradle. A cannula was placed in the left atrium via the superior pulmonary vein so that left atrial pressure could be monitored. Subsequently, a cannula was placed in the ascending aorta and one in the right atrium via the right atrial appendage for cardiopulmonary bypass. Heparin (3 mg/kg, iv) was administered for anticoagulation. If activated clotting time did not exceed 400 seconds (control 100 seconds), supplemental heparin was given. At our institution, all of the above procedures are done routinely in patients undergoing cardiac surgery. Before the patient was placed on cardiopulmonary bypass, a sterile pack containing the doppler probe, the electrical connections, and the suction tubing was opened, and the necessary connections were made. The probe was placed on a coronary vessel, and measurements of phasic coronary velocity and reactive hyperemia were performed. To limit the delay in the operative procedure, in each patient these studies were completed in 15 minutes or less.

Electrocardiogram, mean left atrial pressure, and phasic arterial pressure were monitored continuously during all studies. Measurements of reactive hyperemia were obtained in 13 patients. In 10 patients, the coronary vessel examined with the doppler probe was angiographically normal (Table 1). In three younger patients, ages 12, 15, and 24 (Table 1), the coronary vessels were presumed to be normal.

Selection of coronary vessels was dependent upon accessibility and the angiographic anatomy of the vessel. In many patients, coronary velocity can be measured in right ventricular branches of the right coronary artery, the left anterior descending coronary artery, or one of its diagonal branches. Posterior lateral branches of the circumflex coronary artery and the posterior descending branch of the right coronary artery are inaccessible to our probe. When reactive hyperemia in right ventricular branches of the right coronary artery was examined, the artery was occluded just distal to its point of origin from the parent vessel.

Brief coronary occlusions were accomplished by obstructing the vessel with a vascular forceps just proximal to the probe for 1.5 to 23 seconds. The number of reactive hyperemia responses obtained in each patient varied because of the time constraints and the stability of the probe. Whenever possible, multiple occlusions of variable duration

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**Figure 5** This diagram of a reactive hyperemia response illustrates the manner in which we determined the repayment ratio, the percent increase in peak velocity, and the duration of the coronary occlusion and the reactive hyperemia response.
were performed. Repeated occlusions were usually 30-90 seconds apart. A second occlusion was not performed until velocity returned to baseline.

Statistical Analysis

Data were analyzed using an analysis of variance. Intergroup comparisons were made with Duncan's test. When appropriate, correlation coefficients were calculated. Data are presented as the mean ± 1 SE.

Results

Validation Studies in Dogs

Relationship of Mean Coronary Velocity and Flow

We performed 17-30 paired measurements of mean coronary velocity (doppler) and coronary flow (timed-venous collection) in each of seven dogs. These two parameters correlate closely over a wide range of coronary flows (Fig. 6, left panel). The correlation coefficients in different dogs ranged from 0.93 to 0.97. Similar results were obtained when changes in coronary flow measured with an electromagnetic flow probe were compared with changes in coronary velocity measured with the doppler probe (Fig. 6, right panel).

Simultaneous Measurements of Reactive Hyperemia Responses with the Electromagnetic Floumeter and the Doppler Probe

The phasic characteristics of coronary velocity and coronary flow were remarkably similar in the dog (Fig. 7). In addition, under control conditions, the signals were stable for up to 3 hours. Paired reactive hyperemia curves obtained at variable durations of occlusion were performed in four dogs. The reactive hyperemia curves were qualitatively similar (Fig. 8). The ratio of peak to resting velocity was 9 ± 2% greater than the ratio of peak to resting...
flow (Fig. 9, bottom panel). The correlation between the measurements was $r = 0.94$. The repayment ratios with the doppler system were also $27 \pm 6\%$ greater than those obtained with the electromagnetic flow meter (Fig. 9, middle panel). The correlation between the two measurements was high ($r = 0.90$). The duration of repayment was identical with both systems (Fig. 9, top panel). Comparison of these two methods of measuring coronary reactive hyperemia were similar in all of the dogs examined.

**Studies in Human Subjects**

Clinical data describing the human subjects' heart disease, operative procedure, coronary anatomy and hemodynamic state before and during the coronary velocity studies are presented in Tables 1 and 2. In all, the coronary artery segment examined was either normal or had minimal obstructive disease, and the ventricle perfused by the vessel was hemodynamically normal or probably uninvolved by the subjects' cardiac disease.

The phasic characteristics of coronary velocity in the left anterior descending coronary artery were different from those in the right ventricular branches of the right coronary artery (Fig. 10, A and B). The ratio of diastolic to systolic velocity was greater in the left anterior descending coronary artery than in the right ventricular branches of the right coronary artery [6.5 ± 0.8 vs 2.2 ± 0.4, respectively ($P < 0.05$)]. Because systolic compressive forces are greater in the left than in the right ventricle, the percentage of coronary flow occurring in systole is less.

During the transient coronary occlusions and reactive hyperemia responses, mean arterial pressure changed by less than 5 mm Hg and heart rate changed by less than 5 beats/min. In 6 of 33 transient occlusions, occasional bigeminal premature
ventricular beats occurred. No sustained arrhythmias were provoked. Coronary reactive hyperemia responses were examined in 13 normal coronary vessels of 13 human subjects. The heart rate, mean arterial pressure, and left atrial pressures of the subjects during these studies is shown in Table 2.

In 10 subjects, multiple reactive hyperemia responses were examined following occlusions of variable (1.5-23 seconds) duration. Brief coronary occlusions (less than 2 seconds in duration) always produced hyperemic responses (see Fig. 11, A, and B). Peak responses occurred after 10- to 20-second occlusions in coronary vessels supplying either the right or left ventricles (Fig. 11, A and B).

About half of our subjects had normal coronary vessels (group I, Tables 1 and 2) and half had significant coronary obstructions in vessels other than the one we examined (group II). Since collateral channels could have altered responses in our subjects with associated coronary obstructive disease, we compared the responses of the group I and group II subjects (Table 3). No significant differences between the two groups of responses were noted. To determine whether the quantitative characteristics of coronary reactive hyperemia were different in vessels supplying the right vs. the left ventricle, we compared responses obtained by studying right ventricular branches of the right coronary artery to those obtained by studying the left anterior descending coronary artery (Table 3). No significant differences between the responses obtained in these two groups of vessels were noted.

The relationship between duration of occlusion and the various characteristics of reactive hyperemia are shown in Figure 12. Although responses to 15- to 20-second transient occlusions were obtained in each subject, responses to transient occlusions of other durations were not always available. The relationship between repayment ratio and duration of occlusion is not linear. Maximum repayment ratios occurred with 10- to 15-second coronary occlusions (Figure 12, middle panel). In 7 of 10 subjects in whom responses to transient occlusions of variable duration were available, the repayment ratios were less after a longer occlusion (15-20 seconds) than a shorter one (5-15 seconds). The relationship between peak velocity:resting velocity ratios to duration of occlusion is shown in Figure 12 (bottom panel). The peak to resting velocity ratios following 20- to 23-second occlusions are not significantly less than those following 10- to 15-second occlusions. In 8 of 10 subjects in whom responses to variable durations of occlusion were available, peak velocity:resting velocity ratios obtained at 15- to 20-second occlusions were greater or equal to those obtained with shorter occlusions (Fig. 12, bottom panel). The relationship between duration of response and duration of occlusion is shown in Figure 12 (top panel). With transient occlusions of 20 seconds, the average response duration was 22 seconds. In every subject, the duration of response progressively increased with increases in the duration of occlusion.

Discussion

The major new contributions of our experiments are: (1) development of a method that accurately measures changes in coronary velocity and reactive
FIGURE 9 Results of a quantitative analysis of reactive hyperemia responses obtained with flow and doppler probes in an anesthetized dog. The flow and doppler probes were placed adjacent to one another on the circumflex coronary artery. The integers in the bottom panel indicate the number of reactive hyperemia responses that were averaged for each point. Three quantitative characteristics of reactive hyperemia (repayment ratio, peak velocity: resting velocity ratio and duration of response) are plotted against duration of occlusion. The error bars at each point represent the standard error of the mean. The data indicate that the quantitative characteristics of reactive hyperemia are similar regardless of which method is used to measure the response—an electromagnetic flow probe or the doppler system.

FIGURE 10 A: Simultaneous recordings of mean and phasic coronary velocity, phasic arterial pressure, and the electrocardiogram in a right ventricular branch of the right coronary artery in a human subject. Note that the percentage of the total velocity occurring in diastole is slightly greater than that which occurs in systole. B: Simultaneous recordings of mean and phasic coronary velocity, phasic arterial pressure, and the electrocardiogram in a normal left anterior descending coronary artery. Note that a large percentage of total velocity occurs in diastole in the left anterior descending coronary artery.
TABLE 2  Clinical Characteristics of Subjects at Surgery

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<th>HR (BPM)</th>
<th>Mean PA (mm Hg)</th>
<th>Mean AO (mm Hg)</th>
<th>PaO2 (mm Hg)</th>
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<tr>
<td>LR</td>
<td>Nit, Prop</td>
<td></td>
<td>Hal, N2O, Dz</td>
<td>51</td>
<td>16</td>
<td>65</td>
<td></td>
<td>12.4</td>
</tr>
<tr>
<td>CM</td>
<td>Dig, Prop, Ct</td>
<td></td>
<td>Hal, N2O, Dz</td>
<td>56</td>
<td>69</td>
<td>130</td>
<td>14.8</td>
<td></td>
</tr>
</tbody>
</table>

CM = chronic cardiac medications; Nit = nitrates (usually a combination of sublingual nitroglycerin, nitroglycerate and isosorbide dinitrate); Prop = propranolol; Dig = digoxin; Fr = frusemide; KCl = potassium chloride; Aminoph = aminophylline; Quin = quinidine; Dip = diphyllamine; Dz = diazepam; Sp = scopalamine hydrochloride; A = anesthetic agent; Hal = halothane; N2O = nitrous oxide; Tp = sodium thiopental; Pb = pancuronium bromide; Dz = diazepam; F-D = fentanyl-droperidol; Tc = tubocurarine chloride; Atp = atropine; Ms = morphine sulfate. HR (BPM) = heart rate in beats per minute; Mean PA (mm Hg) = mean left atrial pressure in mm Hg; Mean AO (mm Hg) = mean aortic pressure in mm Hg; PaO2 (mm Hg) = arterial oxygen tension in mm Hg; Hgb (g/dL) = hemoglobin in grams per deciliter.

FIGURE 11  A: Simultaneous recordings of mean coronary velocity and aortic pressure following transient coronary occlusions that vary in duration from 1 to 21 seconds. Note that the transient coronary occlusions are not associated with any significant alteration in arterial pressure or heart rate. Also, the magnitude of the reactive hyperemia response increases progressively as the duration of occlusion increases and appears to be maximal at about a 20-second occlusion. These recordings were obtained in the right ventricular branch of the right coronary artery. B: Simultaneous recordings of mean coronary velocity and aortic pressure following transient occlusions of the left anterior descending coronary artery which vary in duration from 1 to 20 seconds. Note that the transient coronary occlusions are not associated with alterations in arterial pressure, cardiac rhythm or heart rate. Occasionally, isolated premature ventricular beats occur. These responses were obtained in a normal left anterior descending coronary artery.
CIRCULATION RESEARCH

Characteristics of Reactive Hyperemia in Various Subject Subgroups

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>Duration of Occlusion (seconds)</th>
<th>Repayment Ratio</th>
<th>Peak Resting Velocity Ratio</th>
<th>Duration of Response (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (n = 7)</td>
<td>19.4 ± 0.8*</td>
<td>3.5 ± 0.5*</td>
<td>5.5 ± 0.4*</td>
<td>31 ± 3.8*</td>
</tr>
<tr>
<td>Group II (n = 6)</td>
<td>18 ± 1.6</td>
<td>3.4 ± 0.4</td>
<td>6.3 ± 0.8</td>
<td>23 ± 1.4</td>
</tr>
<tr>
<td>RVB-RCA (n = 9)</td>
<td>18.5 ± 1.1†</td>
<td>3.3 ± 0.3†</td>
<td>6.1 ± 0.5†</td>
<td>26 ± 3.2†</td>
</tr>
<tr>
<td>LAD (n = 4)</td>
<td>19.2 ± 1.1</td>
<td>3.8 ± 0.8</td>
<td>5.5 ± 0.9</td>
<td>31 ± 2.3</td>
</tr>
</tbody>
</table>

RVB-RCA = right ventricular branch of right coronary artery; LAD = left anterior descending coronary artery

* Not significantly different from Group II.
† Not significantly different from LAD.

TABLE 3

Peak and resting velocity ratio, and duration of response are plotted against duration of occlusion. The integers in the bottom panel indicate the number of responses that were averaged to obtain each point. These data indicate that coronary reserve in humans is enormous since, on the average, coronary velocity can increase 6-fold in response to the ischemia associated with a 20-second coronary occlusion. Significantly different from the 1-second data (*), 6-second data (†) or 15-second data (‡) at the P < 0.05 level of confidence.

hyperemia and can be applied safely in patients at the time of cardiac surgery and (2) description of the quantitative characteristics of coronary reactive hyperemia in humans.

The discussion section will focus on four areas: the doppler system, problems in the interpretation of the clinical studies, comparison with animal studies, and future implications.

The Doppler Velocity System

Our experiments have addressed two major questions relevant to the applicability of this method—safety and validity.

Safety

There are six potential dangers associated with the use of this method that will be discussed.

The electrical hazards associated with the instrument are negligible. At the frequency excitation that we use (62.5 kHz), arrhythmias cannot be induced even if the wires are attached directly to the heart. Also, the leakage current in the system is low (<50 µA).

The risk of infection associated with the use of the velocity probe is minimized by appropriate sterilization procedures. The instrument is stored in a sealed plastic bag and given to the operating room nurse several minutes before use. The recording machine, doppler meter, and the suction apparatus are not in the operative field.

The material toxicity is minimal. The suction cup is made of a biocompatible transparent plastic. The duration of contact is less than 15 minutes, and the components of the probe are not soluble in body fluids.

Tissue damage could result from two sources: the suction could cause direct mechanical injury or could interfere with myocardial perfusion. Our histological studies performed in dogs have shown that damage to the vasculature and the myocardium from mechanical trauma is negligible even if the probe is left in place for 2–4 hours at maximum suction. Because the probe does not alter regional myocardial perfusion, damage secondary to ischemia, induced by the suction, is excluded.

It is very unlikely that the transient coronary occlusions performed in this study induce myocardial damage. In dogs, coronary occlusion for less than 20 minutes does not cause detectable myocardial necrosis (Jennings et al., 1960). Also, in dogs, transient coronary occlusions (less than 1 min in duration) do not cause sustained alterations in regional myocardial contractility or vascular reactivity (Heyndricks et al., 1975; Bache et al., 1974). These experimental observations are probably relevant to humans because intense coronary spasm of several minutes duration in patients does not produce myocardial necrosis, and the abnormalities in myocardial performance associated with spasm are quickly reversible (Schroeder et al., 1977; Guazzi et al., 1971).

Even if transient coronary occlusions do not cause myocardial necrosis, serious arrhythmias or hemodynamic disturbances could occur. In over 120 subjects, in whom we have performed 350 transient coronary occlusions in 160 coronary vessels, we have not observed any sustained alterations in cardiac rhythm or hemodynamics. We have minimized
the risks of these potential complications by observing the following precautions: (1) human subjects were studied only if the operative procedure was elective and proceeding without difficulty; (2) we performed transient coronary occlusions only on branches of major coronary vessels; (3) we monitored the electrocardiogram, arterial pressure and left atrial pressure during the procedure, and (4) we were prepared to place the subject on cardiopulmonary bypass if necessary. Also, if a transient coronary occlusion produced a significant decrease in mean arterial pressure (>15 mm Hg), increase in left atrial pressure (>5 mm Hg), a change in heart rate (±20 beats/min), or an arrhythmia that was sustained for more than 30 seconds, we planned to discontinue the study. None of these potential hemodynamic disturbances occurred in any of our subjects. All recovered from the surgical procedure uneventfully and were discharged from the hospital.

The studies require that the operative procedure be prolonged by 10-15 minutes. Because measurements of coronary velocity are made prior to cardiopulmonary bypass, the duration of cardiopulmonary bypass—a critical determinant of operative risk—was not altered. Although almost all studies performed in the operative theater prolong the operation, the risks associated with this are probably negligible.

These considerations suggest that the doppler probe provides a reasonable, safe approach to measuring phasic coronary velocity and reactive hyperemia in the coronary circulation of humans.

Validity

Three groups of experiments suggest that our doppler system can measure changes in coronary blood flow accurately. First, phasic coronary velocity and flow tracings are remarkably similar and change in parallel in response to vasoactive stimuli. Second, changes in mean coronary velocity are related closely to changes in coronary flow measured by either timed venous outflow or an electromagnetic flow probe. Furthermore, when flow is zero transiently in systole, velocity is also zero. This indicates that cardiac contractions do not significantly alter the velocity measurements by changing the relationship between the crystal and the stream of blood being examined. Third, the characteristics of reactive hyperemia in the coronary circulation determined with the velocity probe are similar to those obtained with an electromagnetic flowmeter.

Coronary Reactive Hyperemia Responses in Human Subjects

Problems with Interpretation

Interpretation of our data depends on three assumptions: the coronary vessels were normal; coronary velocity prior to the transient occlusion was virtually normal, and the drugs and anesthetics administered to the subjects did not significantly alter coronary vascular resistance or vasodilator responsiveness.

Ten of our subjects had a preoperative coronary arteriogram which showed that the coronary vessel examined was angiographically normal. In three subjects whose age ranged from 12 to 24 years, it is reasonable to presume that the coronary vessels were normal. Furthermore, our analyses indicate that the reactive hyperemia responses in humans with coronary disease in other vessels were not different from those with normal coronary vessels. Also, in all subjects, the ventricle supplied by the coronary vessel studied had either normal or nearly normal hemodynamics. In four subjects with coronary artery disease and normal left ventricular function, we presumed that the right ventricle was normal. None of our subjects had severe pressure-induced cardiac hypertrophy involving the ventricle perfused by the coronary artery examined. Preliminary studies in our laboratory indicate that severe pressure-induced cardiac hypertrophy markedly limits coronary reserve (Marcus et al., 1980).

Since coronary flow was not measured, we must depend on inference to estimate the level of myocardial perfusion prior to the transient coronary occlusions. Metabolic factors (wall stress, heart rate, myocardial contractility, etc.) are the major determinants of coronary flow (Berne and Rubio, 1979). In all of our subjects, heart rate, mean arterial pressure, and right ventricular pressure were near normal. Also, none of the subjects was anemic or hypoxic. Furthermore, thoracotomy and positive pressure ventilation decrease intracardiac volume. This would tend to decrease wall stress and, secondarily, coronary blood flow. Also, halothane, the anesthetic most commonly used in our subjects, is a negative inotropic agent which tends to decrease coronary blood flow. In open-chest dogs anesthetized with halothane, preliminary studies in our laboratory indicate that coronary flow averages 65 ml/min × 100 g, and the ratio of endocardial to epicardial flow is about 1:1. Just prior to cardiopulmonary bypass in subjects anesthetized with halothane, coronary flow measured by the thermal dilution technique is in the normal range (personal communication, Dr. John Moyers, University of Iowa). In view of these considerations, it is likely that coronary flow and velocity were normal in our subjects prior to the transient coronary occlusions.

The anesthetics and other drugs given to our subjects could alter the coronary circulation indirectly by changing hemodynamics or by a direct effect on coronary vascular resistance or vasodilator responsiveness. Since hemodynamics were not markedly altered, indirect effects are of little importance. In addition, we were not aware of data which have shown that the direct effects of these agents alter vasodilator responsiveness to intense metabolic stimulation.
Comparison with Other Studies

The phasic characteristics of coronary velocity reported in this study are similar to those obtained in animals (Coffman and Gregg, 1960; Olsson and Gregg, 1965; Berne and Rubio, 1979) and clinical (Cole and Hartley, 1977; Folts et al., 1979) studies. The coronary reactive hyperemia responses that we observed in human subjects are unique. They demonstrate that the coronary circulation in humans is extremely sensitive to metabolic stimuli and can alter coronary vascular resistance over a 6- to 10-fold range within 5-20 seconds in response to intense ischemia.

Previous measurements of coronary reactive hyperemia in humans have been performed by measuring flow in a bypass graft following transient coronary occlusion of the graft. In most studies (Matthews et al., 1971; Bittar et al., 1972; Greenfield et al., 1972; Olinger et al., 1976; Oldham et al., 1978), a 20-second occlusion usually increased graft flow by 2- to 3-fold. This response was probably limited for three reasons: first, the native vessel was usually not occluded so that magnitude of myocardial ischemia induced by graft closure must have been variable; second, studies were done in diseased vessels following a variable period of cardipulmonary bypass; and, third, obstruction at the proximal or distal sites of anastomosis could have limited the reactive hyperemia response.

Most studies in humans that have measured coronary flow responses to a variety of stimuli (changes in heart rate, arterial pressure, myocardial contractility, drug infusions) have noted increases in coronary flow of less than 100% (Klocke and Wittenberg, 1972; Berne and Rubio, 1979). Since these stimuli evoke relatively feeble vasodilator responses, it is unlikely that they provide a sensitive index of coronary reserve.

Although reactive hyperemia responses that we observed in humans are qualitatively similar to those previously reported in large mammals (Coffman and Gregg, 1960; Olsson and Gregg, 1965; Bache et al., 1974; Berne and Rubio, 1979), there are two quantitative differences. First, with a 20-second coronary occlusion in humans, the ratio of the response to occlusion duration is about one, whereas in animal studies this ratio is greater than two (Coffman and Gregg, 1960; Olsson and Gregg, 1965; Bache et al., 1974; Berne and Rubio, 1979). Second, as a consequence, repayment: debt ratios are lower in humans (usually less than 3-4) than in large mammals (usually about 5-6) even though peak: resting velocity ratios are similar in humans and animals. These differences cannot be explained by methodology since measurements of coronary reactive hyperemia responses with either electromagnetic flow meter or our doppler probe are similar.

There are two potential explanations for these observed differences: the effects of the anesthetic agents employed or fundamental species differences. Animal studies of coronary reactive hyperemia have been performed in awake unseated preparations or in animals anesthetized with anesthetics other than halothane. Most of our subjects were anesthetized with halothane. Because halothane alters both smooth muscle and cardiac muscle, it is possible that some direct or indirect effect of this agent may have shortened the coronary reactive hyperemia responses. Fundamental species differences may explain why coronary reactive hyperemia responses are significantly shorter in humans than in other large animals. For example, if the rate of degradation of the putative mediator of vasodilation was faster in humans than in other large mammals, this would decrease the duration of the response and the repayment:debt ratio without necessarily altering the peak:resting velocity ratios.

Our studies do not shed light on the basic mechanisms responsible for the intense coronary vasodilation that follows transient coronary occlusion. However, in humans, the magnitude of the hyperemic response is coupled closely to the intensity of the metabolic stimulus. The vasodilator responses to very brief occlusions suggest that a myogenic component (Fedor et al., 1978) may play some role in humans.

Implications of These Studies

The method we have described for measuring phasic coronary velocity and reactive hyperemia in humans is easy to apply and safe. In addition, the changes in velocity observed reflect changes in coronary blood flow. Potential applications of the method include studies concerning the effects of physiological factors (heart rate, arterial pressure, changes in contractility), interventions (cardiopulmonary bypass, drugs, operative procedures) and pathological states (aortic stenosis, cardiac failure and congenital heart defects) on phasic coronary velocity and coronary reserve in humans.

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CORONARY REACTIVE HYPEREMIA IN HUMANS/Marcus et al.


Measurements of coronary velocity and reactive hyperemia in the coronary circulation of humans.
M Marcus, C Wright, D Doty, C Eastham, D Laughlin, P Krumm, C Fastenow and M Brody

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