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Research Article

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No correlations were demonstrated between flow and the following: left vs. right grafts, presence or absence of collaterals, total vs. partial block, or the presence or absence of ventricular dyskinesis. In 32 patients, no correlation between these anatomic findings and the presence of reactive hyperemia was demonstrated. In 17 patients, occlusion of the graft for 10 sec resulted in a mean 51.5% flow debt repayment.

In nine patients, injection of 0.3 μg of isoproterenol into the graft increased flow from 45±6 to 69±9 cm^3/min within 4-7 sec without changes in rate, pressure, time derivative of left ventricular pressure (LV dp/dt), or left ventricular end diastolic pressure (LVEDP). Maximum increases to 87±10 cm^3/min occurred 12-20 sec after injection with concomitant changes in these parameters.

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Intravenous infusion of norepinephrine did not change vascular resistance, whereas phenylephrine did. In six patients, injection of 0.2 μg of norepinephrine into the graft decreased flow from 49±6 to 25±5 cm³/min within 5–8 sec.

Intravenous infusion of 0.15 mg of nitroglycerin decreased coronary vascular resistance from 2.7±0.4 to 2.3±0.3 mm Hg/cm³ per min. In five patients, 0.12 mg of nitroglycerin injected into the graft increased flow from 46±7 to 71±13 cm³/min and lasted 20–40 sec.

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INTRODUCTION

The recent use of a saphenous vein aorta-to-coronary bypass graft in patients with coronary artery disease has provided a new and promising approach to the treatment of coronary artery disease (1). The initial clinical results appear to be good (2). Thus, it is imperative to delineate as far as possible anatomic or functional factors which could be used to predict the amount of flow in these grafts and which might relate to their effectiveness. In addition, measurement of phasic flow in the graft provides, for the first time, an opportunity to study some of the mechanisms and drugs which are important in the regulation of coronary blood flow in man. The data given in this report were obtained in 57 patients during the operative procedure for the surgical placement of a saphenous vein aorta-to-coronary graft. Due to the complexity of the operation and difficulty in interpreting data, only patients in whom a single bypass graft was used have been included.

METHODS

Pressure-flow measurements were obtained on 57 patients who had been admitted either to the Duke University Medical Center or the Durham Veterans Administration Hospital for an aorta-to-coronary bypass vein graft procedure. 48 patients were male having a mean age of 48 yr (range 32–65 yr) and 9 were female with a mean age of 52 yr (range 37–59 yr). Data are reported only from patients in whom a single vein graft was implanted since the evaluation of the anatomic relationships to the flow is much less complex than in patients with multiple grafts. In addition, these patients had experienced a shorter period of cardiopulmonary bypass and the effects of pharmacologic agents and experimental procedures could be carried out under more physiologic conditions.

Within a 2 month period before the surgical procedure, each patient had selective cineangiography of the coronary system and opacification of the left ventricle to evaluate ventricular contraction. These cineangiograms were reviewed and the patients grouped according to the following anatomic findings: (*a*) whether the coronary artery was completely occluded or patent proximal to the site where the vein graft was implanted, (*b*) whether collateral circulation into this vessel could be demonstrated, and (*c*) whether any abnormality of left ventricular contraction could be demonstrated.

The majority of the patients were receiving nitroglycerin and/or long-acting nitrites; however, these drugs were not used immediately before or during the surgical procedure. In those patients who were receiving propranolol, the drug was discontinued at least 3 days before the operation.

The operative procedure was carried out essentially according to the technique described by Johnson, Flemma, Lepley, and Ellison (3). The patients were premedicated with secobarbital (100 mg). The anesthetic agents consisted of nitrous oxide and muscle relaxants supplemented by intravenous analgesics, usually morphine. The vein bypass graft was accomplished during extracorporeal circulation employing either a disc or a bubble oxygenator under moderate hypothermia. If a plaque was noted in the distal coronary artery, the graft was fashioned over the plaque so that "bidirectional flow" could be obtained (3).

In the first 11 patients studied, pressure-flow data were recorded during cardiopulmonary bypass and intermittently during the remainder of the operative procedure. These patients demonstrated that blood flow during cardiopulmonary bypass was high and was variable during the first 10 min after bypass was discontinued. In the remaining patients, *control* flow measurements and *all other studies* were carried out just before the closure of the chest (20–30 min after cessation of bypass). At this time, the chest retractor had been partially closed and the surgeons were repairing the groin wound. Thus, the operative field was reasonably undisturbed during the recording of pressure-flow data. Patients who were receiving either pressor drugs or isoproterenol were not studied.

Multiple drugs were not administered to a given patient and usually only one specific intervention was carried out in each patient. The operative procedure was not prolonged by the experiments described in this report and additional risks to the patients were minimized. Untoward results did not occur and none of the studies proved to be in any way injurious to the patient. In approximately 25 additional patients, for various technical reasons, adequate flow measurements could not be recorded. Thus, useful data were obtained in approximately two-thirds of the patients studied.

Blood flow was measured with either a 2.5, 3.0, or 3.5 mm electromagnetic flowmeter probe.[1] The probe was selected to produce a reasonably tight fit but not to significantly occlude the lumen of the vein graft. It was found that the most reproducible flow measurements were obtained when the probe was placed within 2–3 cm of the aortic anastomosis to avoid movement of the probe during cardiac contraction and the resulting changes in flow base line. After placement of the probe, 5–10 min were allowed to elapse so that the probe electrodes could make proper contact and assure recordings of acceptable quality. The electrical zero for flow with which the flowmeter is equipped was found on multiple occasions to be invalid when compared with an occlusive zero and was not used. In order to obtain zero blood flow the graft was occluded 3–5 cm distal to the probe for a brief period before and immediately after any intervention. If the zero had shifted, the data were discarded. Both mean and pulsatile blood flows were recorded. Continuous visual monitoring of the phasic flow configuration allows another check to be sure that the recordings are valid. The flowmeter and probes were calibrated on multiple occasions during the period of use by passing known flows of physiologic saline through the probe during a given period of time. A segment of excised vessel was used for this in vitro calibration. The flow calibration or flow per unit flow signal remained within ±3.5% (SD) and was linear ±2% for the range of flows encountered during the period of use for all probes. In our laboratory good agreement has been found between flow calibrations using this technique and in vivo calibrations using an intact animal.

Both pulsatile and mean arterial pressures were measured through an indwelling catheter placed in the radial artery and connected to a pressure transducer.[2] In a few patients, ascending aortic pressure was measured through an 18 gauge needle connected directly to a similar transducer and inserted into the ascending aorta. In some patients, left ventricular pressure was measured through an 8 cm polyethylene catheter (PE No. 205) placed through the apex of the left ventricle through the vent wound and connected to a similar pressure transducer. The time derivative of left ventricular pressure (LV dp/dt)[3] was obtained using a differentiating network having an undistorted response through 50 Hz. Lead II of a standard electrocardiogram was also recorded during each procedure. Data recordings were made at various speeds on an ink type oscillograph equipped with solid-state amplifiers.[4]

The reactive hyperemic response to a 10 sec period of occlusion of the graft was evaluated in 32 patients. In addition, occlusions of 30 sec and 1 min were evaluated in six and four patients, respectively. In nine patients, 0.3 μg of isoproterenol in 0.1 cm^3 of normal saline was injected directly into the vein graft. In six patients, 0.2 μg of norepinephrine in 0.1 cm^3 of normal saline was injected into the graft. Norepinephrine, 1.0–4.0 μg/min, was infused intravenously in seven patients in order to increase the mean arterial pressure by at least 20 mm Hg. A similar pressure effect was produced in five patients by intravenous infusion of phenylephrine, 0.1–0.3 mg/min. Nitroglycerin, 0.15 mg, was injected as a bolus intravenously in seven patients, and 0.12 mg in 0.1 cm^3 of normal saline was injected into the vein graft in five additional patients. The nitroglycerin was dissolved within 5 min of the time of injection, kept on ice, and sterilized by infusing it through a millipore filter.

In evaluating the data, the mean values of vein graft flow and arterial pressure were measured directly from the respective oscillographic recordings. In like manner, the systolic and diastolic arterial pressure, left ventricular end diastolic pressure (LVEDP), and LV dp/dt were measured. In several patients in whom both the ascending aortic and left ventricular pressures were available, the systolic and diastolic phases of the cardiac cycle were delineated and individual values of both systolic and diastolic vein graft flow were obtained from the phasic flow tracing by

[1] Model RC-1000, Micron Instruments, Inc., Los Angeles, Calif.

[2] P23Db Transducer, Statham Laboratories, Inc., Hato-Rey, Puerto Rico.

[3] *Abbreviations used in this paper:* LV dp/dt, time derivative of left ventricular pressure; LVEDP, left ventricular end diastolic pressure.

[4] Model 7888, Hewlett-Packard Co., Palo Alto, Calif.

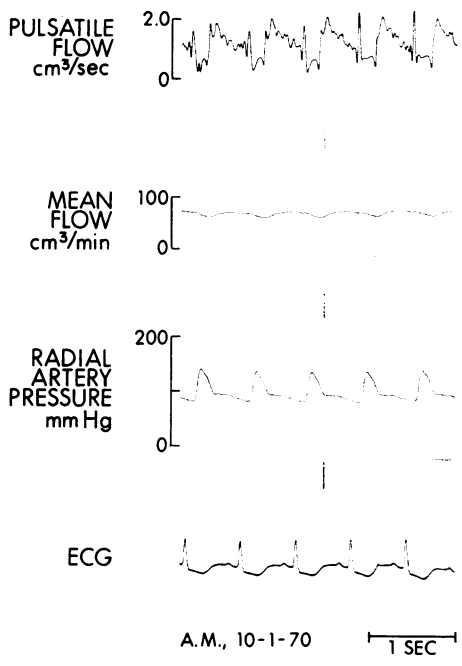

FIGURE 1 A typical example of the pressure and flow recordings obtained in these patients. Note the presence of a transient increase in flow occurring shortly after the onset of systole in the pulsatile flow recording. This transient becomes more prominent in successive beats and is maximal during peak inspiration. The contour of the phasic flow is otherwise similar to that recorded from the left coronary artery of dogs (4, 5).

planimetric integration. Resistance of the vascular bed distal to the vein graft was estimated by dividing the mean arterial pressure in mm Hg by the flow in cm³/min. During the period of reactive hyperemia, the per cent flow debt repayment was computed as the ratio × 100 of the excess in flow (total flow − control flow) which occurred during the period of reactive hyperemia, and the flow deficit (control flow × the duration of occlusion). Standard statistical techniques carried out on a digital computer [5] were used to compare the data.

RESULTS

A typical recording of pulsatile flow in the vein graft appears in the upper rank of Fig. 1. The contour is, in general, similar to phasic flow recorded from the left coronary artery of dogs (4, 5) except for a prominent transient increase in flow occurring shortly after the onset of systole. In Fig. 1 the magnitude of this transient increases in successive beats and is related to respiration, being the most marked at peak inspiration. Note that this finding is also demonstrable in the phasic flow illustrated in Fig. 3 but is not seen in Fig. 6. This finding was present in most of the patients. In two patients in whom the transient was marked, it was noted that the magnitude was much less when the probe was placed near the coronary artery anastomosis.

In five patients, the systolic and diastolic components of the flow were measured from recordings obtained in the control state. The ratio of systolic to total flow ranged from 19 to 34% in these patients.

In Table I, data are summarized from 11 patients who were studied during the period of cardiopulmonary bypass and intermittently during the remainder of the operative procedure. In each patient, the flow was highest during bypass. Approximately 20–30 min after bypass was discontinued, the mean flow for the group stabilized at approximately 60% of the flow during bypass. The higher flow found during bypass could not be related to either a higher heart rate or arterial pressure.

As noted above, *all control flow* measurements and *all other studies* were obtained 20–30 min after the cessation of bypass. At this time, in 42 patients, control measurements were: mean flow 35±2 cm³/min (mean ±SEM). mean arterial pressure 91±2 mm Hg, and heart rate 93±4 beats/min. Arterial blood samples obtained during this time showed a $P_{a_{O_2}}$ of 328±15 mm Hg, $P_{a_{CO_2}}$ 22±6 mm Hg, and a pH of 7.52±0.02. The mean serum potassium was 3.5±0.1 mEq/liter. There was no correlation between the level of mean arterial pressure and the flow. No relation between the age or sex of the patient and the flow could be demonstrated.

In Fig. 2, panel A, the mean flow data is given for these 42 patients divided according to the placement of the graft into either the left or right coronary circulation. The range of flows in both left and right grafts can be seen to be considerable. The average flow in the right coronary graft was 37±3 cm³/min and in the left was 34±3 cm³/min. Obviously, these values are not significantly different. Thus, for the remaining anatomic correlations, both left and right grafts were considered together. In panel B of Fig. 2, the values of flow are divided according to the presence or absence of angiographically demonstrable collateral vessels distal to the point of insertion of the vein graft. Note that no correlation with the flow is demonstrable. In like manner, the flow data are plotted in panel C according to whether a total block of the vessel proximal to the point of anastomosis was present and in panel D, whether the left ventricle was deemed to contract normally or abnormally when evaluated by ventriculography. Again, no significant correlations with these parameters and the flow could be found.

The reactive hyperemic response following a 10 sec occlusion of the vein graft was evaluated in 32 patients. The response was considered to be positive if the maximum mean flow after release was 20% higher than the control flow. In five patients studied during cardiopulmonary bypass, no reactive hyperemic response was found.

[5] Model 1130, International Business Machines Corp., Armonk, N. Y.

TABLE I

Pressure-Flow Data Obtained during and after Cardiopulmonary Bypass

Patient	A					B					C				
		Blood pressure					Blood pressure					Blood pressure			
	Blood flow	Systolic/ diastolic	Mean	Vascular resistance	Heart rate	Blood flow	Systolic/ diastolic	Mean	Vascular resistance	Heart rate	Blood flow	Systolic/ disatolic	Mean	Vascular resistance	Heart rate
	cm³/ min	*mm Hg*	*mm Hg*	*mm Hg/ cm³ per min*	*beats/ min*	*cm³/min*	*mm Hg*	*mm Hg*	*mm Hg/ cm³ per min*	*beats/ min*	*cm³/min*	*mm Hg*	*mm Hg*	*mm Hg/ cm³ per min*	*beats/ min*
M. D. H.	99	—	90	0.9	*	79	110/80	90	1.3	113	64	110/80	72	1.1	102
K. G.	59	—	80	1.4	*	33	100/70	80	2.4	90	21	100/70	80	3.8	90
S. K.	61	—	145	2.4	*	38	145/85	105	2.8	110	46	130/95	107	2.3	93
W. P.	72	—	90	1.3	*	46	120/80	93	2.0	100	42	120/84	96	2.3	96
G. L.	73	—	89	1.2	*	55	129/77	94	1.7	98	41	128/75	93	2.3	96
L. B.	75	128/98	108	1.4	114	55	105/58	74	1.4	100	26	85/50	62	2.4	100
L. D. W.	43	110/80	90	2.1	138	33	110/79	89	2.7	125	26	106/79	81	3.1	125
C. R. S.	43	100/90	93	2.2	120	—	—	—	—	—	32	95/70	78	2.4	109
J. J.	42	110/80	90	2.1	95	34	120/73	89	2.6	100	38	125/95	105	2.8	100
C. G.	33	90/60	70	3.1	87	22	85/55	65	3.0	80	15	80/53	62	4.1	75
A. R. M.	81	115/95	102	1.3	109	68	135/80	98	1.5	92	32	160/88	112	3.5	94
Mean	61±6	109/84	95±6	1.8±0.2	111±7	46±6	116/74	88±4	2.1±0.2	101±4	35±4	113/76	86±5	2.7±0.3	98±4
P						<0.001		N.S.	<0.01	N.S.	<0.001		N.S.	<0.01	N.S.
P											<0.05		N.S.	<0.05	N.S.

Data were obtained during the following periods: (A) during cardiopulmonary bypass; (B) within 10 min after the cessation of bypass; (C) 20–30 min after bypass was discontinued. Below the individual data are listed the mean and ±standard error of the mean (SEM). The *P* values listed in the upper row compare data obtained during period A with those measured in periods B and C and the lower row compares period B with C. N.S. signifies that the differences were not significant ($P > 0.05$). The first five patients (*) had ventricular fibrillation during bypass. The mean flow in this group was 73±7 cm³/min and was 52±9 cm³/min in the six patients in normal sinus rhythm. Although the flow appears to be higher in the patients with ventricular fibrillation, the difference between the groups is not significant ($0.10 > P > 0.05$).

Reactive hyperemia was found in 17 of the 32 patients evaluated. A typical example of the reactive hyperemic response can be seen in Fig. 3. In these 17 patients, the flow debt repayment was 51.5% (range 34.2–75%). The maximum value of mean flow during the period of reactive hyperemia was 155% of the control flow (range 132–173%). In six of these patients, an occlusion of 30 sec was carried out and the flow debt repayment had an average value of 10.6% (range 6.3–18%) and the maximum response averaged 164% (range 119–282%) of the control flow. In four patients, an occlusion of 60 sec was followed by a flow debt repayment of 6% (range 2–13%) with a peak flow of 150% (range 129–181%). The duration of the hyperemic response ranged from 8 to 15 sec and did not correlate with the duration of occlusion. Thus, it can be seen that the hyperemic response was not increased with longer periods of occlusion but tended to decrease. In the 32 patients in whom reactive hyperemia was evaluated, the same anatomic findings as described above were evaluated and appear in Fig. 4. Again, no correlations could be found between the presence or absence of reactive hyperemia and these parameters.

The data obtained in nine patients after the intracoronary injection of 0.3 μg isoproterenol into the vein graft are summarized in Table II. In section B, the flows measured 4–7 sec after the injection are listed. At this time, there was no detectable change in heart rate, LVEDP, and LV dp/dt. The mean flow for the group increased by 53%. In section C of Table II, data are listed which were otbained 12–20 sec after the injection of isoproterenol when the flow had increased maximally. Note that there is a significant increase in heart rate and LV dp/dt and a significant fall in LVEDP. At this time, the flow had increased 93% above the control. 2–5 min elapsed before all parameters returned to control levels.

In Table III, part 1, data measured during the intravenous infusion of norepinephrine in seven patients have been summarized. Note that the increase in mean arterial pressure was accompanied by a concomitant increase in blood flow so tht the vascular resistance did not change significantly. The heart rate was not significantly altered from control values. Similar measurements were obtained during the intravenous infusion of phenylephrine in five patients (Table III, part 2). The increase in mean arterial pressure was not accompanied by a significant change in flow; thus, the computed vascular resistance did increase significantly. However, this response was accompanied by a significant decrease in heart rate. In Table III, part 3, data measured after the intracoronary injection of 0.2 μg of norepinephrine into the vein graft are given. In these six patients, a marked decrease in mean flow occurred, average 49%, from the control values within 5–8 sec without change in any other mea-

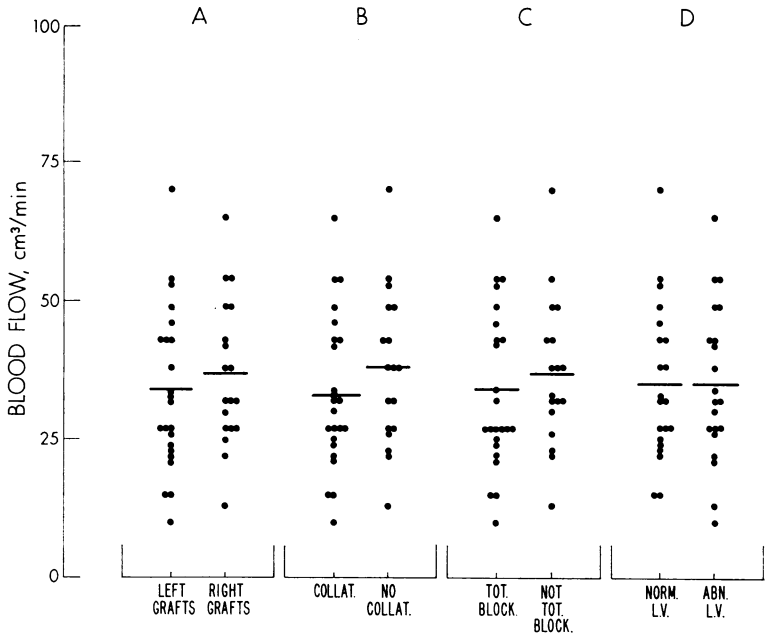

FIGURE 2 Mean flow data from 42 patients grouped according to the notations designated under each column. The bar represents the mean value for each group. Note the wide range of flow and the lack of correlation with any of the anatomic groupings.

sured parameters. The total duration of the reduction in flow persisted for 8–14 sec and then returned to control or slightly higher values. No increases in systemic arterial pressure or heart rate were noted after the intracoronary injection of norepinephrine.

Data obtained after an intravenous bolus of 0.15 mg of nitroglycerin are summarized in Table IV, part 1. A representative recording from one of these patients obtained during the effects produced by nitroglycerin is illustrated in Fig. 5. In these seven patients, an average

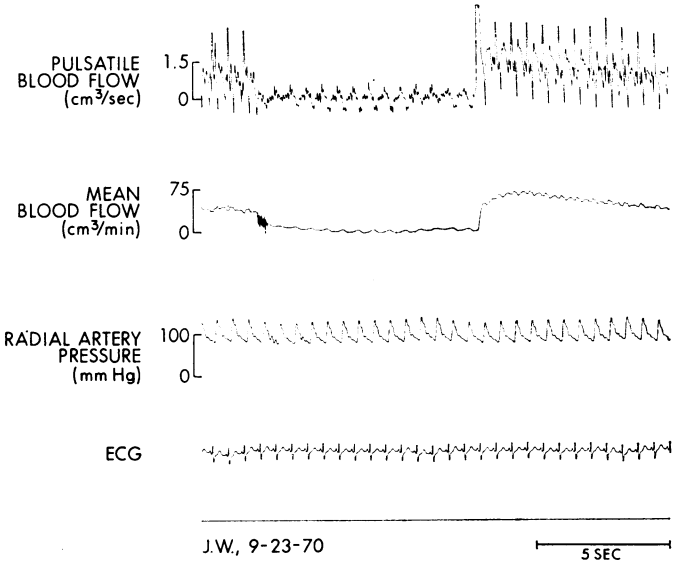

FIGURE 3 A typical example of the reactive hyperemic response to a temporary occlusion of the vein graft which was present in 17 patients. The flow debt repayment in this patient was 54%.

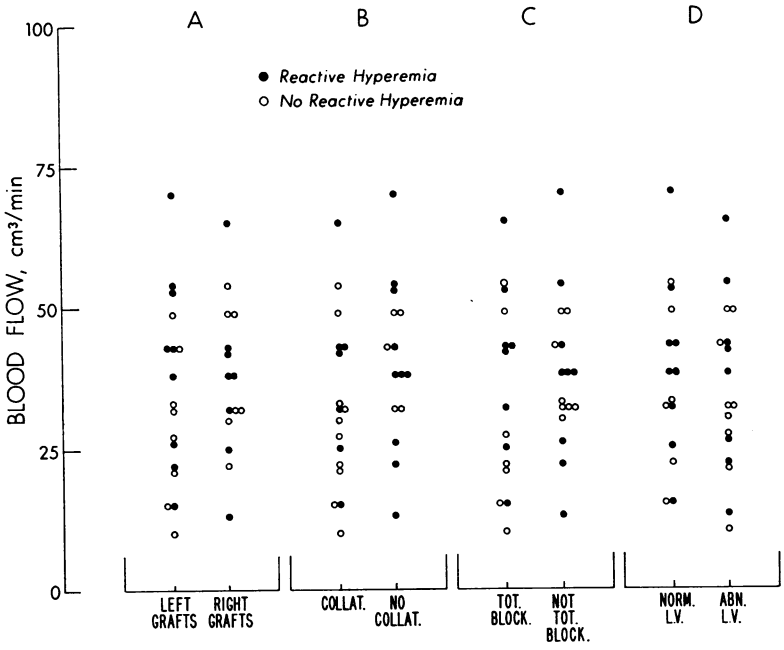

FIGURE 4 Mean flow data from 32 patients grouped according to the designations noted below each column. Patients having a reactive hyperemic response, closed circles, and patients without a response, open circles. Note the lack of correlation between the presence or absence of a reactive hyperemic response and the anatomic groupings.

decrease in mean arterial pressure of 27% was accompanied by an insignificant fall in blood flow; however, in only one patient did the flow actually increase. The vascular resistance significantly decreased. These effects were not associated with a significant change in heart rate. The maximal blood pressure response occurred from 45 to 180 sec after the injection and from 3 to 6 min were required before the control values were

TABLE II

Pressure-Flow Data Obtained after the Intracoronary Injection of Isoproterenol

	A							B	C						
		Blood pressure								Blood pressure					
Patient	Blood flow	Systolic/ diastolic	Mean	Vascular resistance	Heart rate	LVEDP	LV dp/dt	Blood flow	Blood flow	Systolic/ diastolic	Mean	Vascular resistance	Heart rate	LVEDP	LV dp/dt
	cm³/ min	*mm Hg*	*mm Hg*	*mm Hg/ cm³ per min*	*beats/ min*	*mm Hg*	*mm Hg/ sec*	*cm³ min*	*cm³/ min*	*mm Hg*	*mm Hg*	*mm Hg/ cm³ per min*	*beats/ min*	*mm Hg*	*mm Hg/ sec*
M. H.	66	105/58	75	1.1	100	6.5	2100	71	79	105/58	75	0.9	110	5.0	2625
R. C.	81	100/52	68	0.8	105	6.0	1639	108	124	92/72	79	0.6	120	2.0	2622
H. R.	30	114/75	88	2.9	86	9.0	544	44	75	110/75	87	1.2	120	7.0	725
K. S.	38	115/90	98	2.6	97	—	—	80	99	130/95	107	1.1	104	—	—
C. S.	32	95/60	72	2.3	111	5.0	762	65	76	93/60	71	0.9	129	2.5	1039
P. W.	38	120/80	93	2.4	100	7.5	830	56	87	120/84	96	1.1	120	5.0	1304
M. R.	46	120/80	93	2.0	97	—	—	101	132	115/80	92	1.7	101	—	—
C. F. M.	54	135/100	112	2.1	109	7.5	1432	70	81	135/70	90	1.1	109	7.5	1790
W. W.	23	123/75	91	4.0	100	—	—	28	33	145/80	102	3.1	103	—	—
Mean	45±6	114/74	88±5	2.2±0.3	101±3	6.9±0.6	1218±246	69±9	87±10	116/75	89±4	1.3±0.2	113±3	4.8±0.9	1684±329
P								<0.01	<0.01		N.S.	<0.01	<0.01	<0.01	<0.01

Data were recorded during the following periods: (A) control; (B) from 4 to 7 sec after the intragraft injection of 0.3 μg isoproterenol; (C) at the time of maximum flow (12–20 sec after the injection of isoproterenol). At the time the flow measurements were made in B, no change had occurred in the blood pressure, heart rate, left ventricular end diastolic pressure (LVEDP), or the time derivative of left ventricular pressure (LV dp/dt) from the control values. The mean and ±SEM of the individual data are listed. The *P* values compare data obtained during periods B and C with the control data A.

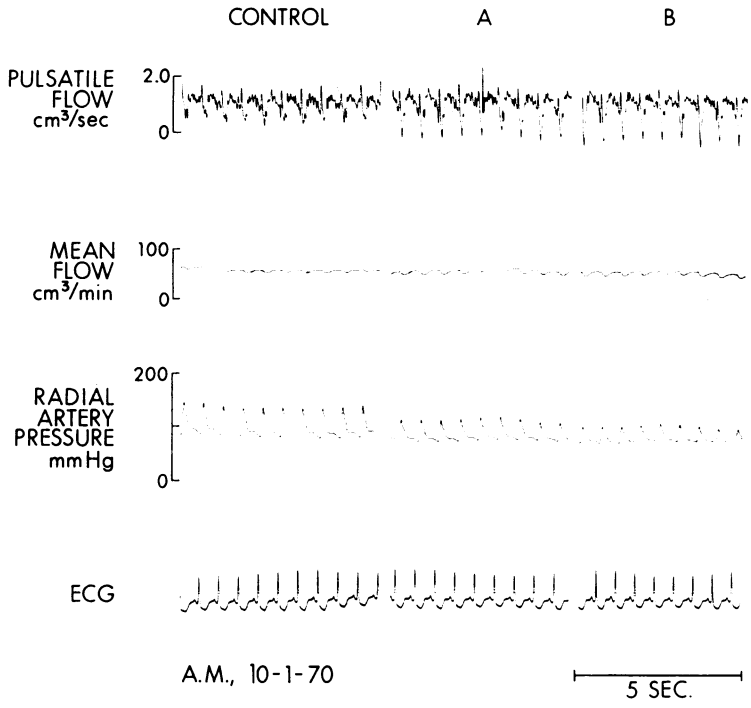

FIGURE 5 A recording obtained after the intravenous bolus of 0.15 mg of nitroglycerin. Recordings in panel A were obtained 45 sec after the injection and, in panel B, 80 sec after injection. The latter represents the maximum decrease in blood pressure. Note that the mean blood flow decreased minimally during the fall in mean arterial pressure.

achieved. In five patients (Table IV, part 2), the intracoronary injection of 0.12 mg of nitroglycerin was accompanied within 4–6 sec by an average increase in flow of 54%. This effect persisted from 20 to 40 sec and was unaccompanied by any concomitant or subsequent changes in arterial pressure. A representative recording is illustrated in Fig. 6. Initially, smaller amounts of nitroglycerin, i.e. 0.01–0.04 mg, were given into the vein graft without any detectable changes in flow.

DISCUSSION

As illustrated by Fig. 1, a transient increase in flow occurs during the initial portion of systole which was most marked when the flow probe was placed near the aortic anastomosis. A possible explanation for this finding is that, concomitant with the onset of systole, rotation of the heart occurs and the vein graft undergoes elongation which momentarily changes the pressure in the graft and results in a rapid influx of blood. This finding was most prominent during peak inspiration when the graft appeared to be maximally stretched. The effects produced by these flow transients on the walls of the vein graft are obviously not known. However, these transients must be considered when evaluating the hemodynamic stresses to which the vein grafts are subjected.

In the left coronary artery of the unanesthetized dog during the control state, the ratio of systolic to total coronary flow ranges from 12 to 20% and becomes greater as the heart rate increases (4). This ratio was found to be somewhat higher (19–34%) during the control state in the five patients in whom it was evaluated. Since the flowmeter probe is placed near the aortic anastomosis, the vein graft, which is distensible, will act as a "capacitor" to damp the true changes in phasic flow which are occurring in the coronary arteries. Thus, calculations requiring a precise measurement of phasic flow are of questionable significance. For this reason, we did not attempt to calculate these data in a large number of patients or during the various interventions.

The finding that blood flow was high during cardiopulmonary bypass is not surprising. Certainly, the obvious explanation is that the heart, which is not mechanically active, will not retard flow during systole in the normal manner. That this is at least partially responsible for this finding is corroborated by the tendency for a higher flow to be present in the fibrillating heart. It should be noted that the high flow during bypass and the increase in flow after isoproterenol infusion clearly indicate that the primary resistance to flow is not in the vein graft or its anastomoses but is in the distal coronary vasculature.

TABLE III

Pressure-Flow Data Obtained after Intravenous Infusion of Norepinephrine, after Intravenous Infusion of Phenylephrine, and after Intracoronary Injection of Norepinephrine

Patient	A					B				
	Blood flow	Blood pressure		Vascular resistance	Heart rate	Blood flow	Blood pressure		Vascular resistance	Heart rate
		Systolic/ diastolic	Mean				Systolic/ diastolic	Mean		
	cm³/min	*mm Hg*	*mm Hg*	*mm Hg/ cm³ per min*	*beats/ min*	*cm³/min*	*mm Hg*	*mm Hg*	*mm Hg/ cm³ per min*	*beats/ min*
1. Intravenous infusion of norepinephrine										
C. E. G.	23	105/68	81	3.6	75	46	220/115	150	3.3	67
W. J.	38	111/73	86	2.4	100	49	151/91	111	2.2	92
L. W.	54	83/50	61	1.1	128	81	125/75	92	1.1	128
F. A.	40	150/78	102	2.6	115	46	185/85	133	2.9	122
C. B.	24	88/62	71	2.9	120	43	164/100	121	2.8	115
E. O.	32	120/72	88	2.8	94	49	175/115	135	2.8	115
P. L.	44	116/72	87	2.0	93	69	180/106	131	1.9	101
Mean	36±4	110/68	82±5	2.5±0.3	104±7	55±5	171/98	125±7	2.4±0.3	106±8
P						<0.01		<0.001	N.S	N.S.
2. Intravenous infusion of phenylephrine										
C. R. G.	13	150/80	103	8.1	72	16	200/105	137	8.6	58
E. S.	32	95/58	70	2.2	100	36	155/93	113	3.1	97
B. J.	34	93/60	71	2.1	77	42	128/80	96	2.3	70
G. S.	32	120/65	83	2.6	70	38	160/85	110	2.9	58
R. H.	32	93/69	77	2.4	83	22	129/84	99	4.6	43
Mean	29±4	110/66	81±6	3.5±1.2	80±5	31±5	154/89	111±7	4.3±1.1	65±9
P						N.S.		<0.01	<0.05	<0.05
3. Intracoronary injection of norepinephrine										
J. W.	46	129/71	90	2.0	100	23	129/71	90	3.9	100
W. D.	49	85/53	63	1.3	67	27	85/53	63	2.3	63
L. G.	54	130/78	95	1.8	100	43	130/75	93	2.2	100
W. F.	68	90/58	69	1.0	92	16	90/58	69	4.3	92
C. F. G.	43	165/90	115	2.7	86	22	165/90	115	5.3	86
M. L.	32	120/80	93	2.9	95	17	120/80	93	5.4	95
Mean	49±6	120/72	87±9	1.9±0.4	88±6	25±5	120/71	87±9	3.9±0.7	87±7
P						<0.01		N.S.	<0.01	N.S.

Part 1. Data were obtained during (A) control, and (B) during the maximum pressure response to intravenously administered norepinephrine. Below the individual data the mean and ±SEM are given.

Part 2. Data were recorded during (A) control, and (B) during the intravenous infusion of phenylephrine. During the response to phenylephrine, patient R.H. received 0.2 mg atropine intravenously. 2 min later flow was 70 cm³/min, blood pressure 168/111, 130 (mean) mm Hg, and the heart rate 94 beats/min. The vascular resistance fell to 1.9 mm Hg/cm³ per min, demonstrating that the increase in resistance during the phenylephrine infusion may have been due to the reflex bradycardia.

Part 3. Data were obtained during (A) control, and (B) the maximum decrease in flow occurring from 5 to 8 sec after the injection of 0.2 μg of norepinephrine into the vein graft. The reduction in flow lasted for 8–14 sec before returning to control or slightly higher values of flow. No change in any of the other measured parameters occurred after the injection of norepinephrine into the vein graft.

The mean value of control flow, 35±2 cm³/min, found in these patients is somewhat lower than recorded in the vein grafts by other investigators (6–8). Johnson, Flemma, and Lepley studied 125 patients and found an average vein flow of 63 cm³/min (6) and Grondin, Lepage, Castonguay, Meere, and Grondin studied 70 patients and found an average flow of 68 cm³/min (7). The reason for the discrepancy is not obvious but may partially be explained by the time in which the flow measurements were made. Johnson et al. (6) made their

TABLE IV

Pressure-Flow Data Obtained after Intravenous Infusion of Nitroglycerin and after Intracoronary Injection of Nitroglycerin

Patient	A					B				
		Blood pressure					Blood pressure			
	Blood flow	Systolic/ diastolic	Mean	Vascular resistance	Heart rate	Blood flow	Systolic/ diastolic	Mean	Vascular resistance	Heart rate
	cm³/min	*mm Hg*	*mm Hg*	*mm Hg/ cm³ per min*	*beats/ min*	*cm³/min*	*mm Hg*	*mm Hg*	*mm Hg/ cm³ per min*	*beats/ min*
1. Intravenous Infusion of Nitroglycerin										
A. M.	54	135/85	102	1.9	95	48	85/65	72	1.5	103
A. A. H.	43	140/80	100	2.1	91	35	80/60	67	1.9	97
C. M.	24	110/68	82	3.4	104	24	95/60	72	3.0	105
J. D.	49	135/73	93	1.9	95	57	100/60	73	1.3	93
A. H.	27	153/88	110	4.1	88	27	105/65	78	2.9	90
P. B.	27	140/93	109	4.0	77	22	93/65	74	3.6	80
J. M.	70	123/83	96	1.4	72	54	95/70	78	1.4	74
Mean	42±7	134/81	100±4	2.7±0.4	89±4	38±6	93/64	73±1	2.3±0.3	92±4
P						N.S.		<0.001	<0.05	N.S.
2. Intracoronary Injection of Nitroglycerin										
H. A.	22	136/88	104	4.7	94	29	136/88	104	3.5	94
L. P.	42	116/72	87	2.1	94	59	116/72	87	1.5	94
C. L.	66	116/66	83	1.2	78	93	116/66	83	0.9	75
D. D.	54	140/80	100	1.9	69	74	140/80	100	1.4	69
R. T.	44	168/96	120	2.7	87	98	168/96	120	1.2	87
Mean	46±7	135/80	99±7	2.5±0.6	84±5	71±13	135/80	99±7	1.7±0.5	84±5
P						<0.05		N.S.	<0.05	N.S.

Part 1. Data were obtained during (A) control, and (B) concomitant with the maximum decrease in blood pressure resulting from an intravenous bolus of 0.15 mg nitroglycerin. The maximum decrease in blood pressure occurred within 45–180 sec and the total duration of the response persisted for 3–6 min.

Part 2. Data were recorded (A) control, and (B) during the maximum increase in flow after the injection of 0.12 mg of nitroglycerin directly into the vein graft. The maximum increase in flow occurred within 4–6 sec and persisted for 20–40 sec before the values returned to control level. No systemic changes in blood pressure were noted after injection of nitroglycerin into the vein graft.

measurements "when the patient's condition has stabilized" and Grondin et al. (7) made their measurements "shortly following cessation of cardiopulmonary bypass." Thus, their results are probably more nearly comparable to our flows measured immediately after bypass. Both of these groups included patients in whom multiple grafts were employed.

It was somewhat surprising that no anatomic or functional correlates with the flow could be delineated (Fig. 2). For example, one might assume that the flow would be greatest in a vessel which was totally obstructed proximally and in which collateral vessels could not be demonstrated. From the data in our study, it would be impossible to predict in which patient a high flow vein graft would be measured during the operative procedure. It is obvious that the subsequent flow in the vein graft may or may not be in any way correlated with the value of flow measured in the acute situation.

A reactive hyperemic response was demonstrated in 17 patients. The nature of this response, however, is markedly different from that obtained in the unanesthetized dog preparation. Occlusion of the left circumflex coronary artery in a group of awake dogs for a 10 sec period resulted in an average change in peak flow of 330% of control, a flow debt repayment of 665%, and a hyperemic response lasting 89 sec (4). The reactive hyperemic response noted in these patients is obviously much less in both magnitude and duration. In addition, longer periods of occlusion in the dog (up to 1 min) result in an increased response with a reasonably constant flow debt repayment. The situation is quite dif-

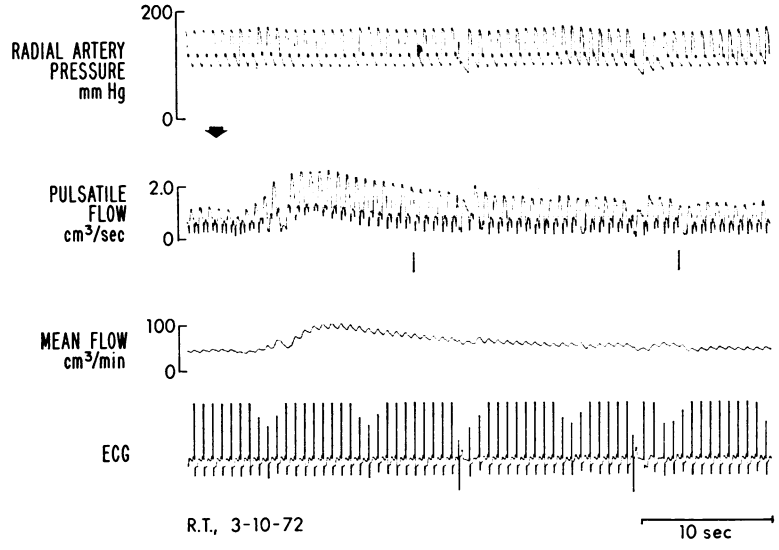

FIGURE 6 Continuous recordings obtained during the direct injection of 0.12 mg of nitroglycerin into the graft. The time of injection is marked by the arrow. Note the marked but brief increase in flow. Arterial pressure and heart rate remained unchanged during the flow response.

ferent in these patients, however, since the flow in the vein graft has only been available to the myocardium for a brief period. Thus, it is not immediately apparent why temporarily stopping this flow should result in a hyperemic response. Reactive hyperemia was not noted during bypass. It may be reasonable to assume that in the patients having reactive hyperemia, collateral vessels which had been supplying the area now perfused through the vein graft have begun to close; and after occlusion of the graft these collaterals do not open with sufficient rapidity to prevent the oxygen debt accumulation and the resulting hyperemic response. That this is the case is strengthened by the fact that longer periods of occlusion result in a decrease in the intensity of the hyperemic response, indicating that collaterals now have opened and are adequately perfusing the myocardium. If this is the correct reason for this observation, it may give some insight into the actual rapidity with which collateral vessels will close and not immediately become functional. As illustrated in Fig. 4, no correlation could be demonstrated between the anatomic or functional parameters and the presence or absence of reactive hyperemia. Again, it seems somewhat surprising, since one might anticipate that an occluded vessel having no demonstrable collaterals might have been more likely to effect a hyperemic response when occluded.

Before proceeding to the discussion of drug effects, it might be well to consider that the vascular resistance as calculated from these data is not an exact analog of resistance calculated for various vascular beds in the usual manner. The pressure-flow relationships in the vein graft may not be identical with those found in the coronary vessels which at least partially perfuse the same vascular bed. For example, the presence of obstructing lesions will limit the flow more at higher flow rates. Thus, one must be careful interpreting the resistance values as indicating only changes in the distal coronary circulation. However, the major trends in vascular resistance should be reasonably consistent with alterations in the tone of the distal coronary vascular bed.

The finding that isoproterenol, when injected into the graft, increases flow very rapidly and before the time any detectable changes occur in the other hemodynamic parameters, clearly demonstrates the presence of beta (vasodilator) receptor activity in the coronary arteries of man. These findings are consistent with similar studies carried out in the unanesthetized dog by Pitt, Elliot, and Gregg (9). The further increase in flow noted in these patients concomitant with the increases in LV dp/dt and the heart rate and fall in LVEDP is consistent with the changes in myocardial oxygen requirements due to the alteration in contractility produced by the drug. In like manner, the immediate fall in flow after injection of norepinephrine into the graft demonstrates the presence of alpha (vasoconstrictor) receptors in the coronary arteries of man. The response noted in these patients was quite marked but of a very short duration. Measurements in three unanesthetized

dogs by Pitt et al. (9) after norepinephrine injection into the coronary artery were variable; in that in one dog the flow 5 sec after injection had increased, in one animal it stayed essentially the same, and in one the flow decreased. After beta receptor blockade with propranolol, the flow decreased after intracoronary administration of norepinephrine (9). In studies on anesthetized dogs, Berne (10) concluded that the primary response to norepinephrine administration was coronary artery vasoconstriction. Our patients obviously were anesthetized and somewhat alkalotic. Whether the difference in response between man and the awake dog is due to a difference in methodology or a true species variation cannot be ascertained. However, it is clear that the coronary arteries of man do contain alpha receptors and that norepinephrine is capable of producing a rather marked vasoconstriction. The difference in the effect on vascular resistance produced by intravenous administration of norepinephrine and phenylephrine in these patients is of interest. However, since in these studies we were unable to control the heart rate, the effect of the bradycardia occurring with phenylephrine in reducing the blood flow secondarily cannot be evaluated. That this was at least partially responsible for the difference in findings was demonstrated by the patient who received atropine during the phenylephrine response which increased the heart rate and flow and decreased vascular resistance below control levels. The data do indicate the relative effect on flow which might occur in a patient in whom these drugs were given therapeutically.

The effects on blood flow and arterial pressure produced by the intravenous administration of nitroglycerin were similar to recordings obtained from anesthetized dogs in our laboratory, except that in the dog, a transient increase in left coronary flow occurs before the decrease in arterial pressure. This findings was not observed in in these patients. A fairly marked decrease in arterial pressure and a significant fall in vascular resistance did occur; however, in only one patient did the flow actually increase. Since the heart rate remained unchanged, the primary hemodynamic effect observed in these patients which might be beneficial in the relief of angina would be a drop in myocardial wall tension with a resulting decrease in myocardial oxygen needs. The injection of a relatively large dose of nitroglycerin directly into the vein graft was required before a direct vasodilating effect could be demonstrated. These findings are in agreement with those recorded by Bernstein, Friesinger, Lichtlen, and Ross (11) who estimated myocardial blood flow after selective injection of xewow[133] into the left coronary artery. These workers found an average increase in myocardial blood flow of 38.5% and a significant fall in coronary vascular resistance 30 sec after administration of 0.1–0.2 mg of nitroglycerin into the coronary artery of five patients having demonstrable coronary artery disease. Obviously, the data obtained in the present studies do not shed any light on the possible redistribution of blood flow perfusion in the myocardium after the sublingual administration of nitroglycerin. That this is the primary effect of nitroglycerin in relieving angina pectoris has been suggested by McGregor and Fam (12). Horwitz, Gorlin, Taylor, and Kemp studied 10 patients during thoracotomy by injecting xewow[133] into the subepicardium in diseased areas of the left ventricular wall and measuring the subsequent washout rate (13). These investigators found that nitroglycerin administered sublingually increased the flow in nine patients and concluded that nitroglycerin improved the perfusion in areas of diseased myocardium. In their study, seven patients were receiving an infusion of phenylephrine and the blood pressure did not decrease after nitroglycerin administration. Thus, the results are not strictly comparable to those obtained in patients taking nitroglycerin therapeutically.

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