Effect of Cardiac Contraction on Coronary Blood Flow

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In the experimental animal the basic and controversial problem was studied of the influence of cardiac contraction on coronary blood flow. Normally beating hearts were perfused at a constant pressure, and coronary inflow and outflow were determined. In order to assess the role of systole, prolonged periods of ventricular asystole and fibrillation were induced and observations were made of the changes in coronary flow. With the cessation of cardiac contraction blood flow in the coronary arteries and coronary sinus rose appreciably. The results of these studies support the concept that contraction of the heart muscle, by compression of the myocardial vascular bed, behaves as a throttling mechanism and impedes coronary flow. The method employed permits a separation and quantitation of the effects on coronary flow resulting from cardiac contraction and the vasomotor state of the coronary vessels.

THE effect of organized cardiac contraction on flow through the capillary bed of the myocardium remains unsettled despite much work that has been done to elucidate this basic problem. Evidence has accumulated in support of 2 opposing viewpoints. One concept is that the shortening of the muscle fibers during systole compresses the vascular bed in the myocardium and acts as a "throttling" mechanism. The opposing view is that cardiac contraction "massages" or "kneads" the blood through the vascular bed and increases coronary flow. The primary objective in this study has been an evaluation of the effect of organized myocardial contraction on coronary flow in the intact animal. This problem has been attacked by the elimination of this factor by the induction of ventricular asystole or ventricular fibrillation. Comparisons have been made of coronary flow in the beating heart perfused at a constant pressure with those in the nonbeating heart under the same conditions.

METHODS

Twenty-seven adult mongrel dogs were anesthetized with intravenous pentobarbital (25 mg./Kg.). Respiration was maintained through an endotracheal tube connected to a demand-valve apparatus supplied with oxygen. The left chest was entered through the fourth intercostal space and the pericardium was opened. The appropriate coronary vessels were than cannulated. The left coronary artery was dissected at its origin from the aorta and a specially designed brass cannula was inserted into it via the left subclavian artery and tied securely in place by means of a ligature. For study of the right, circumflex, or descending branches of the coronary arteries, the vessel was dissected and ligated close to its origin. A small glass or polyethylene cannula was inserted into the distal end for perfusion. For flow measurement in the coronary sinus a flexible polyvinyl catheter was introduced through the right atrial appendage into the sinus and maintained in place at its orifice by a suture ligature. A rotameter was placed in the circuit, and blood was returned to the superior vena cava via the external jugular vein. In some experiments blood was allowed to drain from the coronary sinus catheter to the atmosphere. Mean coronary arterial pressure was determined by use of a Statham strain gage.* A diagrammatic illustration of the experimental preparation is shown in figure 1.

Blood entering the coronary artery was first passed through a recording rotameter[1] connected to a carotid artery and between experimental observations this vessel supplied the coronary perfusion. For a short time prior to induction of asystole and during this period, blood was perfused from a reservoir at or near the prevailing mean aortic pressure. Heparin was used as an anticoagulant (200 mg. initially and 100 mg. each 30 min.). In some instances this was supplemented by pontamine-fast pink (150 mg./Kg. initially and each hour thereafter) or Treburon (35 mg./Kg. and 125 mg. each hour thereafter). Asystole was produced by direct stimulation of both vagus nerves in the neck with an Electrodyne stimulator† delivering 250 volts at a

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* Manufactured by Statham Instruments, Inc., Hato Rey, Puerto Rico.

† Manufactured by Electrodyne Co., Endicott St., Norwood, Mass.

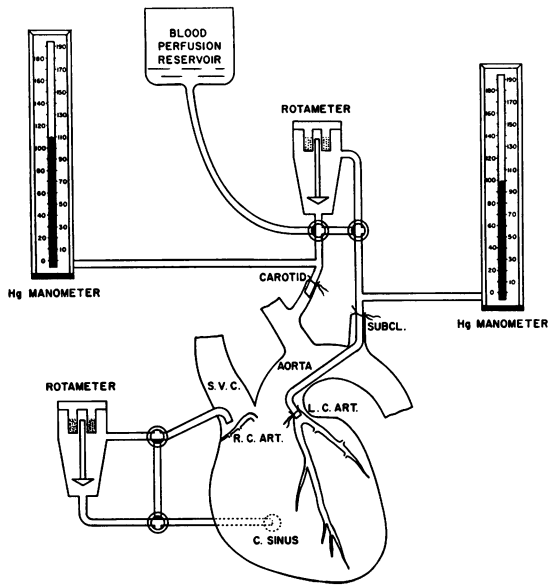

FIG. 1. Diagrammatic illustration of experimental preparation. A metal cannula was inserted in the left coronary artery and a polyvinyl catheter was sutured into the coronary sinus. Both were connected to rotameters for continuous recording of arterial inflow and venous outflow. The left coronary artery was perfused from the blood reservoir at a constant pressure.

frequency of 30/sec. This stimulus resulted in a period of asystole of 4 to 26 sec. Ventricular fibrillation was induced by direct stimulation of the left ventricle with an inductorium. A continuous recording of aortic and coronary perfusion pressure and coronary arterial and venous flow was obtained with an oscillograph.

RESULTS

A total of 248 observations of coronary flow with the heart in either asystole or ventricular fibrillation was made as follows:

Left Coronary Artery Inflow in Ventricular Asystole. There were 4 animals in which flow through the left coronary artery was studied and 40 inductions of prolonged asystole were performed. In each instance there was a rise in coronary flow after the onset of asystole. The average control flow was 93 ml./min. and following asystole it rose to 141 ml./min., representing an increase of 59 per cent (table 1). Maximal flow was reached in 1 to 4 sec. and remained elevated, although there was usually a slight fall with time. (In 2 later experiments in an unrelated study, coronary flow rose with asystole but fell later to a value below that of the control. Such a response was thought to be abnormal and probably the result of partial obstruction of the coronary sinus.)

TABLE 1.— *Flow in Left Coronary Artery and in Left Circumflex Coronary Artery in Ventricular Asystole*

Dog no.	Number of determinations	Average control flow ml./min.	Average flow during asystole ml./min.	Per cent increase in flow
Left coronary artery				
1	11	149	218	46
2	10	82	113	38
3	15	45	95	111
4	4	97	139	43
Average.....		93	141	59
Left circumflex coronary artery				
1	12	27	35	30
2	12	51	66	29
3	9	30	41	37
4	17	36	59	64
5	14	39	64	64
6	24	37	63	70
7	11	21	43	105
8	7	56	77	38
9	9	50	68	36
10	20	53	75	42
11	16	57	84	47
12	9	59	81	37
13	11	27	41	52
Average.....		42	61	50

Flow in a Left Coronary Artery Branch and in the Right Coronary Artery During Ventricular Asystole. The possibility was investigated of a difference in response of the coronary bed supplied by the right coronary artery or a major branch of the left coronary artery from that of the main left coronary artery. Two experiments were done with cannulation of both the right and left coronary arteries. Typical results during 1 of these experiments is shown in figure 2. Both right and left coronary arterial flows rose simultaneously, indicating that the beds supplied by these vessels respond in a similar manner during asystole.

A total of 171 determinations in 13 animals were made of coronary flow in the circumflex branch of the left coronary artery during ventricular asystole. In every instance flow rose

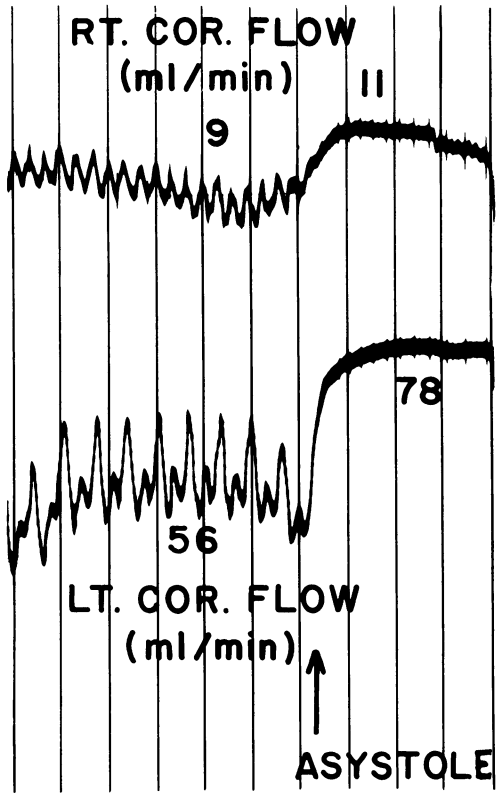

FIG. 2. Record illustrating flows in both right and left coronary artery. With the induction of asystole, flow increased in the left coronary artery from 56 to 78 ml./min. and in the right coronary artery from 9 to 11 ml./min. The time lines are 1 sec. apart.

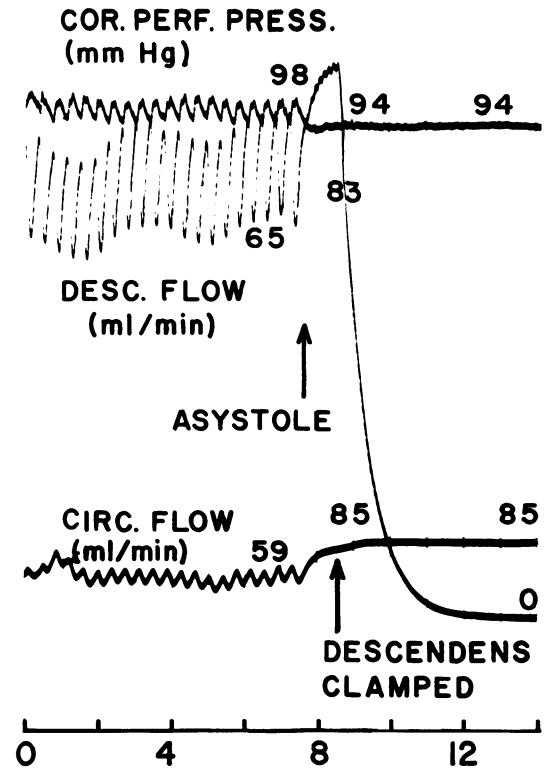

FIG. 3. Record showing control flows in circumflex (59 ml./min.) and descendens (65 ml./min.) arteries with a perfusion pressure of 98 mm. Hg. With induction of asystole flow in both vessels rose to 85 and 98 ml./min. respectively. When the descendens was occluded, circumflex flow remained constant. The record shows 7 seconds of asystole. Abscissa, time in seconds.

in the vessel as it was perfused at the preasystolic mean aortic pressure level. The average flow before asystole was 42 ml./min. and following asystole the value rose to 61 ml./min., representing an increase of 50 per cent (table 1). A typical record of the rise in circumflex flow during asystole is shown in figure 3.

Left Coronary Artery Inflow and Coronary Sinus Drainage in Asystole. In 3 animals, 6 determinations of both the left coronary arterial inflow and coronary sinus drainage were recorded during asystole while coronary perfusion was maintained at a constant pressure. Coronary arterial flow was always increased during asystole (31 to 77 per cent), with an average increase of 50 per cent. In each instance except 1, coronary sinus flow was also increased (table 2). Typically, there was an initial fall in coronary sinus drainage for 2 to 3 sec. and then it rose to exceed control values (fig. 4).

Coronary Arterial Inflow and Coronary Sinus Drainage in Ventricular Fibrillation. In 5 animals, a total of 8 simultaneous determinations of flow through the left coronary artery and the coronary sinus was made before and after the onset of ventricular fibrillation (table 3). The coronary inflow rose from 11 to 72 per cent, with an average increase of 26 per cent. The rise of flow in the coronary sinus varied from 16 to 76 per cent, with an average of 37 per cent. A typical record illustrating the increase in both arterial inflow and venous drainage is shown in figure 5. A rise in arterial flow in both the circumflex and descendens branches of the left coronary artery is also shown to occur with ventricular fibrillation.

The possibility must be considered that a portion of the augmentation of coronary inflow

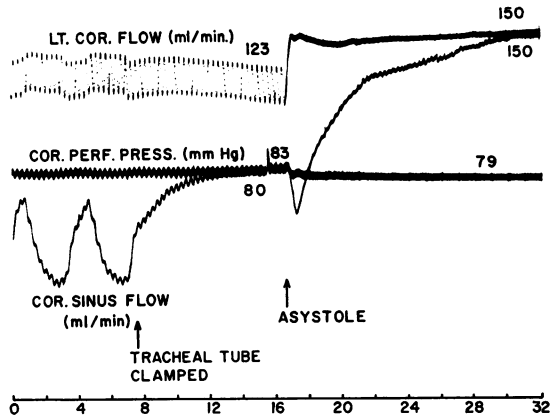

FIG. 4. Record illustrating control flow in left coronary artery (123 ml./min.) and in coronary sinus (80 ml./min.) with a perfusion pressure of 83 mm. Hg. During asystole both flows rose (coronary artery to 150 and coronary sinus to 150 ml./min.) at a perfusion pressure of 79 mm. Hg. The endotracheal tube was clamped prior to asystole to eliminate respiratory variations in coronary sinus flow. Abscissa, time in seconds.

TABLE 2.—*Left Coronary Artery and Coronary Sinus Flow in Ventricular Asystole*

No.	Left circumflex flow			Coronary sinus flow		
	Control (ml./min.)	In asystole (ml./min.)	Per cent increase	Control (ml./min.)	In asystole (ml./min.)	Per cent increase
1	119	156	31	72	86	19
	111	151	36	68	80	18
2	94	166	77	38	59	55
	105	168	60	62	52	−16
	95	142	49	34	48	41
3	142	209	47	94	108	15
Average			50			30

TABLE 3.—*Left Coronary Artery and Coronary Sinus Drainage in Ventricular Fibrillation*

No.	Left coronary artery flow			Coronary sinus flow		
	Control (ml./min.)	V. Fib. (ml./min.)	Per cent increase	Control (ml./min.)	V. Fib. (ml./min.)	Per cent increase
1	89	126	42	56	74	32
	103	119	16	68	88	30
2	123	145	18	38	45	18
	132	147	11	40	51	28
3	119	139	17	74	119	61
	124	146	18	86	151	76
4	134	159	19	82	114	39
5	81	139	72	43	50	16
Average			26			37

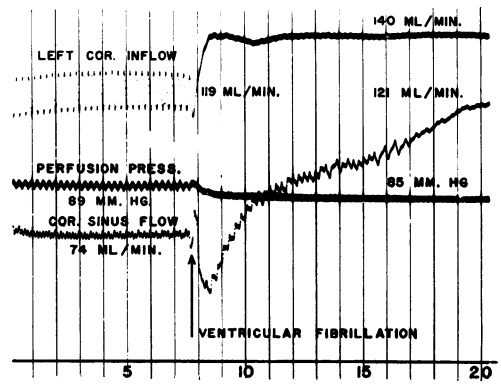

FIG. 5. Record illustrating flow changes in the left coronary artery and coronary sinus during ventricular fibrillation. Flow rose in the left coronary artery from 119 to 140 ml./min. and in the coronary sinus from 74 to 121 ml./min. Perfusion pressure remained essentially constant at 85 to 89 mm. Hg. Time lines are 1 sec. apart and are numbered on abscissa.

with removal of coordinated ventricular contraction is related to events other than prolongation of the period of diastole. During asystole the central pressure and flow in a coronary artery or branch not perfused from the constant pressure reservoir decrease during induced asystole. In most dog hearts collateral channels exist between the coronary arteries and their branches. Accordingly, experiments were performed to test whether a portion of the increase of coronary inflow in the perfused coronary artery with vagal stimulation or with ventricular fibrillation arises from passage of blood to the nonperfused vessel by these channels. A total of 23 determinations on 3 animals were performed in which flow in the circumflex and descendens branches was determined following clamping of one or the other after the induction of asystole (fig. 3). As the descendens artery was clamped and its flow fell to 0, no appreciable rise occurred in the circumflex flow. The reverse was also true, that is, when the circumflex was clamped there was no appreciable rise in flow through the descendens coronary bed. Similarly, clamping of either the right coronary artery or a branch of the left coronary artery during asystole did not affect flow through the other coronary artery. Fi-

nally, occlusion of the circumflex branch following fibrillation did not significantly alter flow in the descendens branch.

It is considered unlikely that in these experiments vagal stimulation per se affected coronary inflow in any way other than by mechanical removal of myocardial contractions because, within 1 sec. or less from the onset of stimulation, coronary flow reached its new level where it was maintained during asystole. Similarly, application of electrodes to the ventricle to induce fibrillation did not appear in itself to affect coronary flow, since repeated ventricular stimulation by this means during ventricular fibrillation did not alter coronary flow.

Discussion

For nearly 3 centuries physiologists have debated the question of the direction and magnitude of the effect of ventricular systole on coronary blood flow. In 1689 Scaramucci expressed the view that the coronary vessels filled during ventricular relaxation and emptied during ventricular contraction.[2] The names of Thebesius, Vieussens, and Morgagni are associated with those who maintained that the coronary arteries are prevented from filling during systole due to closure of their orifices by the aortic valves.[3] While now all agree that the latter mechanism is untenable, there is much less certainty regarding the *net* effect of organized contraction of cardiac muscle fibers on coronary blood flow. With skeletal muscle the analogous situation is more clearly understood and the experimental results have been in closer agreement. Many observers have reported increased venous outflow during the contraction of this type of muscle. Blalock first made simultaneous observations of arterial inflow and venous drainage in the gastrocnemius before, during, and after contraction.[4] These studies clearly demonstrated a reduction in flow in the artery during contraction with a corresponding increase in venous flow. By use of the technic of direct transillumination Knisely and associates[5] have observed flow in the capillary bed of the frog and its relationship to muscular contraction. It was observed that the striated muscle fibers became wider and compressed the capillaries enough to stop flow at the beginning of a powerful contraction. As individual fibers began to relax flow began again. Studies on the myocardial vascular bed with this technic have shown compression of the capillaries by ventricular contraction to the point of erythrocyte standstill.

The importance of ventricular systole in the control of coronary flow is illustrated in a number of studies. In the left coronary artery perfused during systole at a pressure approximately equal to the prevailing mean aortic pressure, arterial inflow approaches 0.[7] Other studies have shown that for an equivalent time period, left coronary artery systolic inflow is less than diastolic inflow.[7-9] These observations lend support to the concept that organized ventricular contraction results in diminished coronary flow. However, in other studies the systolic flow in the coronary sinus has been observed to be much greater than the diastolic flow, which might suggest that ventricular systole augments coronary flow,[10] and coronary sinus drainage has been noted to decrease during ventricular fibrillation.[11] From the available data there is evident a lack of agreement as to the *net* effect of systolic contraction on flow in the coronary bed.

It is a difficult task to assess the factor of the extravascular myocardial support, and several groups of investigators have made attempts to evaluate its role in the regulation of flow in the heart-lung preparation. Various methods have been employed in an effort to clarify this problem. Hilton and Eichholtz,[12] Hammouda and Kinosita,[13] and Anrep and Hausler[14] have employed ventricular fibrillation to remove, at least in part, the effect of cardiac contraction and have determined the changes that occur in coronary flow. These investigators found that in this preparation coronary arterial inflow increased during fibrillation. In contradistinction to this, Osher[15] in studying the pressure-coronary sinus flow relationships of perfused hearts both beating and fibrillating found a decreased flow during ventricular fibrillation. Garcia Ramos[11] also noted less flow during ventricular fibrillation in the isolated mammalian heart perfused by the circulating blood of another animal. Recently Wiggers[10] has presented an evaluation of the effect of ventric-

ular contraction on coronary flow by integrating phasic flow curves recorded from the coronary sinus. Measurements were made of instantaneous flow in the coronary sinus in late diastole when the effects of myocardial compression and volume elasticity were minimal. From these data it was concluded that systole results in an augmentation in coronary flow. The validity of an analysis based upon phasic flow data rests upon the assumption that flow in the epicardial arteries and veins represents actual flow in the myocardial capillary bed. This point remains to be proved.

A method has been devised in the present studies that is thought to measure separately the magnitude and direction of the effect of mechanical ventricular activity on flow through the coronary bed and that also permits simultaneous quantitation of the vasomotor state of the coronary vessels. This method consists essentially of the simultaneous recording of blood flow in the left coronary artery and coronary sinus together with the mean coronary perfusion pressure and mean aortic pressure. The coronary system was perfused at a constant pressure approximating the prevailing mean aortic pressure and measurements were made in the normally beating heart and then during ventricular asystole induced by vagal stimulation. The possible effect of vagal stimulation per se on the coronary vessels is a factor deserving comment. Anrep[3] has shown that section of the vagi leads to an increase in coronary flow even when the heart rate is kept constant. Stimulation of the peripheral end of the vagus with rhythmically interrupted faradic current resulted in a slower heart rate with little change in coronary flow during the first 30 sec. Flow than began to diminish, reaching a minimum in 1 to 1½ min. The important point relative to the studies reported here is that vagal stimulation would not be expected to have a direct intrinsic effect on the vessel wall that would result in an *increase* in coronary flow. A flow change, if any, would presumably be opposite in direction from that following the reduction or removal of the extravascular support. For comparison, similar determinations were made before and after ventricular fibrillation and it was demonstrated that coronary flow was increased under the latter circumstances.

The induction of ventricular asystole invariably has been associated with a marked rise in coronary arterial inflow and coronary sinus drainage. The level of coronary flow reached during ventricular asystole is thought to represent that due to the vasomotor state of the coronary bed alone at the prevailing aortic pressure, and the increase in flow that occurs during asystole to indicate the magnitude and direction of the effect of myocardial contraction on blood flow through the myocardial wall. Trends of the same direction but of smaller magnitude occurred when the ventricle was in a state of fibrillation.

Summary

Coronary arterial inflow and coronary sinus drainage have been determined in the perfused heart in both the beating state and after withdrawal of the extravascular support by the induction of asystole or ventricular fibrillation. The removal of the extravascular support by this means invariably resulted in an increase in flow in the coronary arterial bed and in the venous drainage from the coronary sinus. Evidence is presented to advance the concept that the *net* effect of ventricular contraction is to impede coronary flow. Contrariwise, the removal of this factor results in an increase in flow through the myocardial vascular bed. It is believed that this approach supplies a method for the separation and quantitation of the effects on the left coronary flow of myocardial contraction and of the smooth muscle in the walls of the coronary vessels.

Summario in Interlingua

Le influxo del arteria coronari e le drainage del sino coronari esseva determinate in le corde perfundite, tanto in le stato de pulsation como etiam post le elimination del supporto extravascular per le induction de asystole o fibrillation ventricular. Le elimination del supporto extravascular per iste medio resultava invariabilemente in un augmento del fluxo in le vasculatura del arteria coronari e in le drainage venose ab le sino coronari. Es presentate datos que supporta le concepto que

le effecto *nette* del contraction ventricular es un impedimento del fluxo coronari. Inversemente, le elimination de iste factor resulta in un augmento del fluxo in le vasculatura myocardial. Nos opina que iste puncto de vista permitte le disveloppamento de un methodo pro le separation e quantitation del effectos exercite super le fluxo coronari sinistre per le contraction myocardial e per le musculo lisie in le parietes del vasos coronari.

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The earliest writings of men who later became prominent are always of great interest to those who concern themselves with the development of genius. One thinks of Osler's "Christmas and the Microscope," Lister's "Observations on the Contractile Tissue of the Iris," of Humphry Davy's "Nitrous Oxide," published when he was twenty-two, and of many others.

William Withering's medical thesis, De angina gangraenosa, published at Edinburgh when he was twenty-five years of age, is likewise peculiarly interesting because it proclaims him a keen observer and a man who had gained unusual clinical wisdom early in life.—JOHN F. FULTON. *The Place of William Withering in Scientific Medicine.* J. Hist. Med. & Allied Sc., **8:** 16, 1953.