Regional Myocardial Blood Flow after Sudden Aortic Constriction in Awake Dogs

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SUMMARY  Hemodynamic and regional myocardial blood flow responses were studied 5 seconds (early) and 30 seconds (late) after abrupt proximal aortic constriction in chronically instrumented awake dogs. During the early phase, left ventricular end-diastolic pressure (LVEDP) increased and stroke volume (SV) decreased significantly. During the late phase, there was a positive inotropic response manifested by a decrease in LVEDP and increase in SV (Anrep effect). The late inotropic response was closely associated with a recovery from subendocardial underperfusion. Hemodynamic and regional flow responses after β-adrenergic blockade with propranolol (0.4 mg/kg) were similar to those observed during control. Studies during coronary vasodilation induced by adenosine (0.75-1.0 mg/kg per minute) showed that, if subendocardial flow was elevated during the early phase, the early increase of LVEDP and decrease of SV were less than control; however, if subendocardial flow did not change from control in the early phase and did not subsequently increase, there was no late inotropic response. These data suggest that the Anrep effect in the awake dog is closely related to a recovery from subendocardial ischemia.

IN 1912, ANREP observed that sudden aortic constriction resulted in left ventricular dilation followed by partial recovery while the systolic arterial pressure was maintained at a constant level (Anrep effect). Patterson et al. noted that an increase in coronary flow was associated with this positive inotropic response and suggested that the recovery phenomenon was due to an “improvement of nourishment of the ventricle.” Later it was shown that the Anrep effect is independent of total coronary flow, and this observation led several investigators to question Starling’s original hypothesis and to suggest that the Anrep effect is an intrinsic property of cardiac muscle and a form of autoregulation similar to the Bowditch effect. More recently, Monroe et al. and Gamble et al. strengthened Starling’s original hypothesis by presenting convincing evidence that the Anrep effect is due to recovery from subendocardial ischemia as documented by regional myocardial blood flow, as well as intracavitary electrocardiographic and myocardial oxygen tension recordings in an isolated heart preparation.

Although insight into the mechanisms of the ventricular response to acute aortic constriction has been gained from studies in heart-lung preparations, the hemodynamic characteristics have not been adequately described in the awake anesthetized state. Since the variables of anesthesia, tachycardia, and autonomic tone have been shown clearly to substantially influence the response to acute pressure overload in the closed-chest dog, the significance of examining the Anrep effect in the awake, resting state is apparent.

The purpose of this study was to characterize the hemodynamic and regional myocardial blood flow responses to sudden aortic constriction in the awake, unanesthetized dog. In addition, the extent to which these responses are modified by β blockade with propranolol and vasodilation induced by adenosine was analyzed. A close relationship between the presence of subendocardial underperfusion and ventricular decompensation following sudden aortic constriction was demonstrated.

Methods

Complete studies were obtained on 12 healthy mongrel dogs weighing 20-30 kg. They were anesthetized with sodium thiamylal (30-40 mg/kg, iv) and underwent left thoracotomy via the fourth left intercostal space. The ascending aorta was dissected free, and a Statham TT-Q electromagnetic flow probe was positioned just distal to the aortic valve, as previously described. A specially designed silastic pneumatic occluder having an inflatable inner bladder reinforced with a stainless steel backing was used. This occluder had been carefully designed and pretested to ensure progressive closure of the vascular lumen (Hazem Everett Co.). It was placed 2 cm distal to the aortic flow probe and separated from the probe by a strip of silastic sponge. The proximal 2 cm of the left circumflex coronary artery was dissected free and a Statham type ST electromagnetic flow probe was positioned around the vessel proximal to any branches and stabilized. A polyvinyl pneumatic cuff occluder was positioned just distal to the coronary probe. A bipolar pacing electrode was secured to the right atrium. Polyvinyl chloride catheters 3 mm in outer diameter were filled with heparin and inserted into the left atrial cavity via the left appendage, the left ventricle via a stab wound in the apex, and the aorta via the left internal mammary artery. The aortic catheters were positioned just distal to the aortic flow...
The leads from the flow probes, the ends of the pressure catheters and occluders, and the pacing leads were stabilized with the ends tunneled into a dorsal subcutaneous pouch at the base of the neck for easy access and protection from damage.

An interval of 7–14 days was allowed for full recovery of the dogs before the studies were performed. At this time, the dogs were free of infection and anemia, and showed no evidence of ill health. Since extreme rapid elevations in ventricular afterload may induce acute valvular insufficiency and thereby obscure the magnitude of the late inotropic response, left ventricular and aortic cineangiograms were performed on the day prior to the study, using a Siemens unit equipped with image intensification. Aortic constriction was instituted to acutely increase aortic systolic pressure by approximately 60 mm Hg. Either aortic or mitral valve regurgitation was demonstrated in five dogs which were excluded from further study. In the remaining 12 dogs, no cineangiographic evidence of valvular insufficiency could be detected.

On the day of the study, the occluder, catheters, and leads were exteriorized from the subcutaneous pouch, using 2% lidocaine local anesthesia. The dogs were loosely restrained and studied while awake and resting quietly on their right sides. The laboratory was dimly illuminated and kept free of noise or other activity that might disturb the dogs. Aortic and left ventricular pressure catheters were attached to Statham P23Db transducers and zeroed at the mid-chest level. Aortic and coronary flows were measured with a Statham M-4000 electromagnetic flowmeter. Prior to the study, flowmeter calibrations were performed in vitro by passing known amounts of normal saline through the probes in a given period of time. Both high and low flow rates were measured to test linearity. The coronary and aortic probe calibrations remained within a range of ± 1.25% and ± 3.0%, respectively, throughout the series of experiments. Pressures, flows, and lead II of the standard electrocardiogram were recorded on both an eight-channel magnetic tape recorder and an eight-channel direct-writing oscillograph.

After all recording instruments were connected, a 30-minute interval was allowed for the dogs to adjust to laboratory conditions. Continuous monitoring of pressures and flows was performed throughout the study to ensure that steady state conditions were attained prior to each data sampling period. Following the recording of control hemodynamic data, aortic constriction sufficient to raise left ventricular systolic pressure approximately 60 mm Hg was initiated within one to two cardiac cycles and maintained for 45 seconds. Aortic constriction during sinus rhythm resulted in a prompt increase in heart rate of approximately 20–30 beats/min. Thus, to eliminate any rate-related effects on regional myocardial flow or other hemodynamic parameters, atrial pacing was performed during the data collection to provide a constant heart rate. In each study, hemodynamic data were recorded continuously for a 5- to 10-minute period before constriction was begun, during constriction, and for 5–10 minutes after release.

Regional myocardial blood flow was measured by injections of carbonized radioactive microspheres, 7–10 μm, labeled with four β-emitting nuclides (51Cr, 141Ce, 85Sr, and 46Sc). The microspheres were obtained as 1 mCi of each nuclide in 10 ml of 10% dextran and 0.05% polysorbate 80. The stock solution was diluted in 10% dextran so that the volume injected, 1.0 ml, contained approximately 3 million microspheres. Before each injection, the microspheres were thoroughly mixed by alternate agitation in an ultrasonic bath and vortex agitator for at least 15 minutes. Over a 2- to 3-second period, 1.0 ml of the microsphere mixture was injected into the left atrium and flushed immediately with approximately 6 ml of room temperature saline. During each injection, a reference sample was collected from the aortic arch at a known flow rate via the ascending aortic catheter. Collection of the reference sample began simultaneously with the onset of the injection of microspheres.

By this procedure, regional myocardial blood flow was measured 5 and 30 seconds after aortic constriction. Blood flow determinations were made during the early and late phases on sequential and hemodynamically identical responses to aortic constriction. Seven dogs were studied under control conditions, and four dogs were studied 10 minutes after propranolol infusion (0.4 mg/kg, iv). The adequacy of β blockade with propranolol was verified by the absence of an increase in stroke volume and heart rate after challenge with intravenous isoproterenol, 3 μg/min. In six dogs, regional myocardial blood flow was measured 5 and 30 seconds after aortic constriction during infusion of adenosine, 0.75–1.0 mg/kg per minute, an amount sufficient to abolish the reactive hyperemic response to a 10-second coronary occlusion. If the proximal diastolic aortic pressure fell below 50 mm Hg during the early phase 5 seconds after aortic constriction, the adenosine infusion rate was adjusted to maintain a diastolic aortic pressure greater than 50 mm Hg. The adenosine infusion was maintained for 5 minutes before injection of microspheres to achieve steady state conditions during the hemodynamic study. Previous studies from our laboratory have shown that, during maximum vasodilation with adenosine, the radioactivity found in 10-ml samples of coronary sinus blood obtained during a microsphere injection is less than 1.0% of the corresponding radioactivity found in the left ventricle.

At the end of each study, the dog was killed, and the heart was removed and placed in 10% formalin for a 3- to 6-day period to facilitate sectioning. The atrial tissue, right ventricle, pericardial fat, and large epicardial coronary vessels were dissected from the left ventricle and discarded. The left ventricle was divided into four transverse rings parallel to the mitral valve annulus. The middle two rings were divided then into six regional areas: anterior, septal, posterior, posterior papillary, lateral, and anterior papillary. Each regional area was divided into four nearly equal layers from epicardium (layer 1) to endocardium (layer 4). The majority of the samples were between 1 and 2 g. The myocardial and blood reference samples were counted in a γ spectrometer at optimum window settings selected to correspond to the peak energies of each radioactive nuclide. The counts per minute
The hemodynamic changes following a sudden aortic constriction are summarized in Table 1. In 12 dogs during control conditions, an abrupt increase in left ventricular systolic pressure from 134 ± 5 mm Hg (resting) to 201 ± 8 mm Hg (early) was observed (P < 0.01) over the period of two to three consecutive heart beats. The changes in systolic pressure were accompanied by a marked increase in left ventricular end-diastolic pressure from a resting value of 10 ± 1 mm Hg to 28 ± 2 mm Hg during the early phase. This was followed by a decrease to 19 ± 1 mm Hg in the late phase as the systolic pressure was maintained constant. Concomitantly, the left ventricular stroke volume significantly decreased from a resting value of 14.7 ± 1.2 ml/min to 6.7 ± 0.9 ml/min during the early phase and then significantly increased to 14.2 ± 1.1 ml/min during the late phase. During the early phase, the aortic electromagnetic flowmeter recording demonstrated no retrograde flow during diastole, indicating the absence of aortic valvular insufficiency. A variable transient decrease in aortic diastolic pressure occurred in the early phase (range, 8–26 mm Hg; mean, 20 mm Hg); however, in the late phase, the aortic diastolic pressure significantly increased to exceed resting levels (P < 0.05). The above data describe a ventricular response to a sudden aortic constriction, characterized by early decomposition followed by late recovery.

The responses to aortic constriction were compared during three phases: (1) test—immediately prior to aortic constriction, (2) early—approximately 5 seconds after aortic constriction was begun, and (3) late—approximately 30 seconds after initiation of aortic constriction. The average hemodynamic values for five successive beats were used for each phase. Hemodynamic measurements were made on a minimum of three separate responses to aortic constriction for each intervention. Stroke volume was obtained by planimetry of the phasic aortic flow recordings. Left ventricular and aortic pressures were measured directly from the oscillograph recordings. Stroke work, g/cm, was calculated as the product of stroke volume and mean systolic pressure. The tension-time index (TTI) was obtained by planimetry of the area under the left ventricular pressure curve during the period of ejection. The diastolic pressure-time index (DPTI) was obtained by planimetry of the area under the proximal aortic pressure during diastole and subtracting the area under the left ventricular pressure curve during diastole. Data were analyzed by Student’s t-test for paired data, using an IBM 1130 digital computer.

Results

The hemodynamic changes following a sudden aortic constriction are illustrated in Figure 1. The mean myocardial blood flow during control conditions in seven dogs in the early phase following aortic constriction was 1.18 ± 0.11 ml/min per g (panel A). There was a transmural gradation of flow during the early phase, and subendocardial flow was significantly less than subepicardial, 0.39 ± 0.09 ml/min per g, as compared to 1.54 ± 0.13 ml/min per g, respectively (P < 0.05). During the late phase, mean flow significantly increased to 1.92 ± 0.09 ml/min per g (P < 0.05) (as compared to the early phase); subendocardial flow markedly increased to 1.85 ± 0.22 ml/min per g (P < 0.05), whereas subepicardial flow did not change significantly.

Panel B shows that the regional myocardial blood flow responses following propranolol were directionally similar to controls. There was a significant increase in mean myocardial flow from 0.88 ± 0.13 (early) to 1.30 ± 0.12 ml/min per g during the late phase (P < 0.05) and a marked increase in subendocardial flow from 0.26 ± 0.13 (early) to 1.31 ± 0.15 ml/min per g (late) (P < 0.05). There was no significant change in subepicardial flow.

Figure 2 illustrates the two contrasting effects that occurred in the regional flow responses during adenosine infusion for the group I and II dogs. In group I, during the early phase the mean myocardial blood flow was 2.09 ±
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Hemodynamic data are shown for three phases. Data labeled R were obtained in the resting state immediately prior to aortic constriction, data labeled E were obtained 5 seconds after aortic constriction, and data labeled L were collected approximately 30 seconds after initiation of aortic constriction, corresponding to the time of the maximum inotropic response. All values are reported as mean ± SEM. N refers to the number of dogs. The P values shown under the E column represent a comparison between the early and the resting phase, and the P values under the L column represent a comparison between the late phase and early phase. NS signifies that the P value was >0.05. There was no significant difference between hemodynamic responses during control and after propranolol administration in resting, early, or late phases in four dogs (P > 0.05). The hemodynamic responses to adenosine are separated in two distinct groups of three dogs each, group I and group II. P values were not obtained to compare the adenosine groups with control because of the small sample size.
Regional myocardial blood flow responses are presented. The ordinate shows myocardial blood flow in ml/min per g, and the abscissa shows the layer of the myocardium sampled. The left ventricular myocardium was divided into four equal portions with layer 1 representing epicardium and layer 4 representing the endocardium. The mean value is the average of the four layers and represents the mean blood flow through the ventricular wall. The solid line connecting the filled symbols represents regional myocardial blood flow during the early phase, 5 seconds after aortic constriction, and corresponds to the hemodynamic and coronary flow data labeled E in Table 1. The data represented by the stippled line connecting the open symbols represent myocardial blood flow during the late phase, approximately 30 seconds after aortic constriction, and correspond to the hemodynamic flow data labeled L in Table 1. The asterisks indicate that P < 0.05 when early and late flows for mean and each of the four myocardial layers were compared. In panel A, regional myocardial blood flow responses are illustrated for seven dogs studied during control conditions. Panel B represents regional myocardial blood flow for four dogs studied 10 minutes after propranolol, 0.4 mg/kg.

0.42 ml/min per g, significantly elevated above control, and there was a marked transmural gradient from a subepicardial flow of 3.95 ± 0.76 to a subendocardial flow of 0.53 ± 0.15 ml/min per g. There was, however, no significant change in either mean or subendocardial flow during the late phase. In group II, the mean myocardial flow during the early phase was 3.76 ± 0.53 ml/min per g and was substantially higher than the mean flow observed during either control, Figure 1, panel A, or group I. In group II there was a transmural flow gradient with subepicardial flow of 5.65 ± 0.63 ml/min per g and subendocardial flow of 1.05 ± 0.03 ml/min per g. During the late phase, subendocardial flow increased to 2.03 ± 0.20 ml/min per g, while subepicardial flow decreased slightly, resulting in a slight increase in mean transmural flow.

It is worthy of note that during the early phase the subendocardial flow in group II was higher than either the control or group I: 1.05 ± 0.03 as compared to 0.39 ± 0.09 and 0.53 ± 0.15 ml/min per g, respectively. Subendocardial flows during the late phase for the control and group II dogs were not significantly different. In addition, during the late phase, mean flows through the ventricular wall were closely similar for the control and group I dogs; however, the regional distribution and the amount of subendocardial flow were markedly different. A homogenous distribution through the ventricular wall was observed in the control group, while an uneven distribution was observed in group I with less flow to the subendocardium as compared to the subepicardium.

In the four dogs treated with propranolol and in two additional dogs that received propranolol, but in which regional flow was not measured, there appeared to be a hypercontractile state manifested by a "reverse ANrep" effect. Stroke work and coronary blood flow were compared prior to aortic constriction and after the release of constriction at a time when left ventricular end-diastolic pressure had returned to control levels (Fig. 3). At 20–30 seconds after release, both coronary blood flow and stroke work were significantly elevated as compared to preconstriction values. The increased stroke work suggests that contractility was enhanced following release of aortic constriction, because both heart rate and left ventricular end-diastolic pressure were not significantly different from preconstriction values.

It has been suggested that the presence of subendocardial ischemia may be predicted by the ratio of the diastolic pressure-time index (an estimate of available blood supply to the subendocardium) to the tension-time index (an
The objective of the present study was to determine whether the regional myocardial blood flow responses following a sudden aortic constriction would support the hypothesis that the Anrep effect as seen in the awake dog is essentially a recovery from subendocardial ischemia. The data show that, under control conditions, the early phase of ventricular decompensation is associated with a transmural gradation of flow with marked subendocardial underperfusion that is clearly different from the slight gradient of flow across the ventricular wall favoring the subendocardium previously reported for the awake dog in the resting state. Presumably, the sudden increase in ventricular pressure results in elevated transmural pressures which have been reported to be highest in the subendocardium, and thus gives rise to the reduced subendocardial flow during the early phase. In addition, in these awake dogs, the diastolic aortic pressure fell during the early phase after sudden aortic constriction, resulting in a decreased diastolic perfusion pressure which has been shown previously to be a major determinant of subendocardial flow. In the late phase of ventricular recovery, subendocardial flow increased markedly to exceed subepicardial flow. This was associated with an increase in the diastolic aortic pressure which would favor flow to the subendocardium.

Our data afford two interpretations for the mechanism responsible for ventricular recovery after aortic constriction. The first offers the explanation of a primary reversal of the endo/epi flow ratio mediated by coronary vascular autoregulation with resultant reduction in subendocardial ischemia and consequent increases in stroke volume which lead to a secondary but favorable increase in diastolic aortic pressure. The alternate explanation is that ventricular recovery and increased subendocardial perfusion are the direct result of increased diastolic aortic pressure mediated by peripheral vasoconstriction. We would suggest that the former interpretation is more likely for the following reasons: (1) the time course of changes in stroke volume apparently preceded changes in diastolic aortic pressure in the majority of dogs, (2) the preservation of the Anrep effect in the isolated heart preparation when the diastolic perfusion pressure is maintained constant after an abrupt increase in systolic pressure.

Beta-adrenergic blockage with propranolol, 0.4 mg/kg, did not alter significantly the hemodynamic or regional myocardial blood flow responses following sudden aortic constriction, a result consistent with findings of Vatner et al. This would argue against a reflex sympathetic effect from a baroreceptor mechanism as providing a major stimulus for the improvement of ventricular contractile state during the late phase. In addition, the preservation of the late increase in subendocardial flow as well as the late recovery phenomenon in the presence of β-blockade indicates that the mechanism of coronary vascular autoregulation was not significantly impaired by β-blockade.

Analysis of the regional myocardial blood flow and hemodynamic responses in the dogs studied during vasodilation induced by adenosine provides additional insight into the importance of subendocardial perfusion. Infusion of adenosine in submaximal doses which elevated mean myocardial flow twofold above control did not prevent subendocardial underperfusion during the early phase and did not significantly change the amount of early ventricular decompensation. It did, however, prevent later increases in subendocardial flow and was associated with no late ventricular recovery. This effect may have been accentuated by the low aortic diastolic pressure which did not increase in the late phase in these adenosine-treated dogs. This would suggest that, under certain conditions, vasodilators may potentially inhibit coronary autoregulation.

Discussion

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tion. In contrast, adenosine in high doses that elevated mean myocardial flow 4-fold significantly increased subendocardial flow during the early phase, as compared to control, and afforded a degree of protection to the ventricle against early decomposition following aortic constriction. The apparent question of how a higher effective dose of adenosine did not prevent autoregulation from occurring, whereas a lower dose did, cannot be answered easily. Certainly, in the dogs that were protected, the rise in aortic diastolic pressure in the late phase partially contributed to the late increase in subendocardial flow. In addition, one may speculate that the early protection allowed the ventricle to recover in the presence of maximal vasodilation.

Previous studies by Monroe et al., using ATP as a coronary vasodilator, have revealed complete abolition of the Anrep effect in an isolated heart preparation. The levels of coronary flow induced by ATP were very high, and the abolition of the Anrep effect may have been due to complete lack of subendocardial ischemia in the early phase, as the authors have suggested. In addition, the isolated heart preparation allowed a greater control of the aortic diastolic pressure and avoided the complication of a reduction in diastolic perfusion pressure. One could speculate that if enough adenosine were administered to raise subendocardial flows in the early phase to those values obtained during the late phase in control conditions as an adequate perfusion pressure was maintained, complete protection might be achieved in the awake animal. The question of whether an increase in coronary flow is capable of producing a positive inotropic response is controversial. Previous studies document that a positive inotropic response accompanies an increase in coronary flow. Furthermore, vasodilators which are not known to have positive inotropic effects in muscle strip preparations induce such effects in isolated heart preparations. There is evidence from the isolated heart that the vasodilation which accompanies an increase in perfusion pressure has a positive inotropic effect. In addition, in the isolated heart preparation, a "reverse Anrep" effect characterized by both a left ventricular end-diastolic pressure and a ventricular circumference less than control has been observed when ventricular pressure is suddenly lowered and coronary flow remains elevated. In the present study a "reverse Anrep" effect occurred, manifested by a hyper-
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