THE CAPACITY OF THE CORONARY BED IN CARDIAC HYPERTROPHY

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Until diodrast clearance was used to study renal blood flow, there was no yardstick of normal blood flow through human organs during life to compare with the rates of flow observed during perfusion postmortem. It now is evident that the studies of renal perfusibility carried out soon after death with aqueous solutions yielded values, at 100 mm. Hg, only 10 to 40 per cent as great as the flow calculated for young adult male kidneys excreting diodrast. On the other hand, waiting until rigor passes off, perfusing at high pressure to break up rigor, and using kerosene as a perfusion fluid yields values, at 100 mm. Hg, well above diodrast clearances (1). It therefore seemed worth while to use the same technique on the coronary arteries in hope of obtaining information on the vascular bed of hypertrophied hearts to supplement that obtained by morphological studies (2).

Methods

The technique was essentially the same described for kidneys (1). The cannulae, thin walled, metal, and of the largest, snug fitting caliber, were introduced through the ostia in the aortic wall; heavy enterostomy clamps on the auricles cut off much flow through this tissue, prevented leaks, but were so placed as not to interfere with the coronary venous return. Good checks were usually obtained at 160 and 100 mm. Hg after initial perfusion with one liter at 200 mm. In the heart more often than in the kidney the second pair of observations indicated no change or slight slowing of flow rather than slightly faster flow. The arterial bed was visualized by roentgenograms after injecting lead-gelatin at 40°C., chilling, and opening by Schlesinger's method (3). Perfusion and injection of lead-gelatin increased the weight of the heart; from the weights before and after study of intact hearts, and before and after removing the auricles and great vessels, it was found that the ventricular weight equalled 65 to 74 per cent of the final heart weight. The calculated ventricular weights of most hearts were taken as 70 per cent of the final heart weights.

As in the case of the kidneys, the results were all calculated on the conventional assumption that the pressure at the entrance to the coronary ostia was the same as that in the pressure bottle. Since the perfusion system always offers some resistance this assumption, which seems to be universal in studies of organ perfusion, introduces

a systematic error which is largest in cases with rapid flow and thus tends to increase the spread between high and low rates. In the heart perfusions a U tube connected to the two cannulae, and the system, without cannulae or other resistance gave a rate of flow, at 100 mm. Hg of 3200 cc. per minute; resistance ($R = P/F$) of 0.031. In a small heart, with total flow 490 and flow per gm. of 2.9 cc. per minute, recalculation after subtracting R of the perfusion system from observed R works out thus: 0.204 $-$ 0.031 = 0.173; ideal flow = $\frac{100}{0.173}$ = 580 cc. per minute; flow per gm. = 3.4. The usual calculation gives an error of -18 per cent. With a very fast flow and large heart, where total flow was 910 cc., flow per gm., 1.5 cc., the corrected figures are 1260 and 2.1 cc. Here the error is -40 per cent. It will be apparent from these examples that the figures for flow, calculated and recorded below in the conventional way, are too low by 20 to 40 per cent if one wishes to calculate the true resistance or flow capacity of the vascular bed of an organ. The uncorrected figures only are given, in order to keep the results comparable to those of other workers and in other organs. The only previous report on coronary perfusion gives no figures for heart weight (4) or flow per gram, but the total rates for flow of serum through the hearts of adults dying of infectious disease appear to be about one-fourth as great as those now reported.

RESULTS

In addition to the observations on normal hearts and hypertrophied hearts without gross narrowing of coronary arteries, these other data were obtained:—

Normal young dog, flow at 100 mm. Hg, 8.1 cc. per gm. per minute in a heart weighing 40 gm. Two old dogs, with marked renal hypertension and hypertrophied hearts, 125 gm. heart, flow 3.75 cc. per gm. per minute; 140 gm. heart 2.3 cc. per gm. per minute. Gollwitzer-Meier (5) reported blood flow rates up to 2 cc. and Harrison (6) up to 5 cc. per gm. per minute in living dogs.

In infants, at 6 weeks 3.2 cc. per gm. per minute, at 18 months 5.2, and at 27 months 6 cc. per gm. per minute.

In two patients with narrowing but no occlusion of the coronaries 0.8 and 0.95 cc. per gm. per minute at 100 mm. Hg. In another, with one main branch very narrow and two branches occluded, with large fibrous scars and small recent infarcts, 0.3 cc. per gm. per minute.

The resistance to flow (Pressure/Flow) was greater at 100 mm. than at 160. The rise in resistance at the lower pressure was 8.6 per cent in those under 60 years old, and slightly less, 6.5 per cent, in those between 60 and 89. There was no significant difference between those 40 to 60 and the younger group. Apparently the rigidity of the vessel walls is increased more in senility than in non-senile elderly persons. With perfectly rigid walls the resistance is the same at all pressures and the actual difference noted represents a 25 per cent increase in rigidity.

Other results are summarized in Figs. 1 to 3.

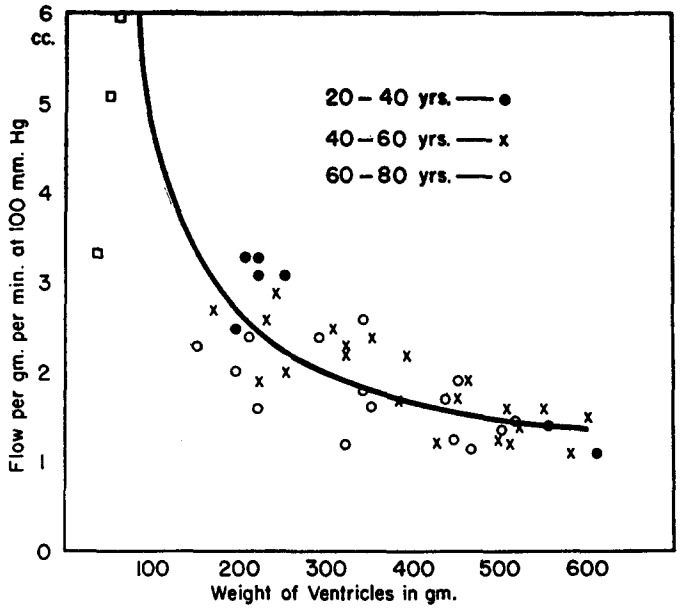

FIG. 1. All data on kerosene perfusion of human hearts postmortem. □ = infants 6 to 27 months, ● = adults of 20 to 40 years, × = adults 40 to 60 years, ○ = adults 60 to 80 years. No cases with coronary narrowing demonstrable by x-ray of heart after injection of lead-gelatin are included. The heavy line, roughly relating flow to heart weight, has the formula $F = 0.7 + 400/W$.

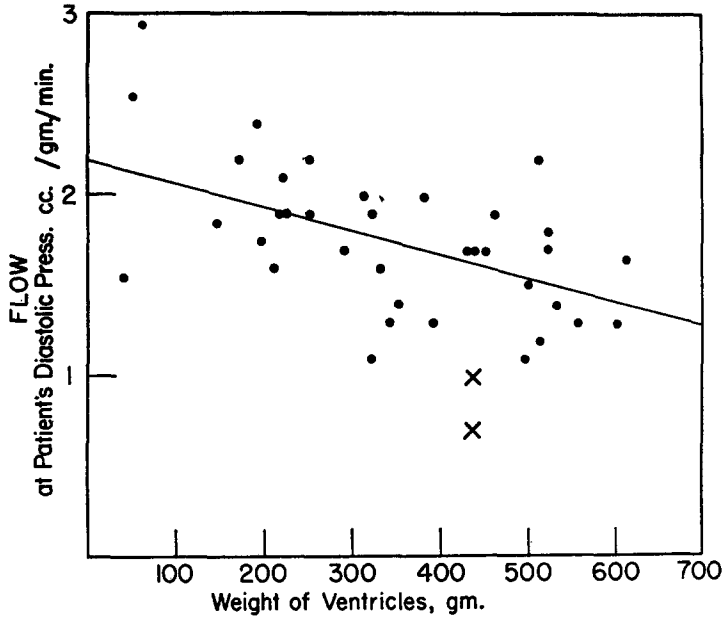

FIG. 2. Kerosene perfusion flow at patient's diastolic pressure. This includes all observations on cases with repeated blood pressure observations for some time prior to terminal illness. The diastolic pressures of the three infants were arbitrarily taken as 55 mm. Hg, and in all cases diastolic flow calculated by multiplying flow at 100 mm. Hg by diastolic pressure divided by 100. × = cases of aortic insufficiency with low diastolic pressure.

Age.—Age has a very striking effect on the vascular bed, even in hearts of the same weight and when all are free from coronary narrowing due to atheroma. In hearts of normal weight (ventricular weights of 150 to 250 gm.) the

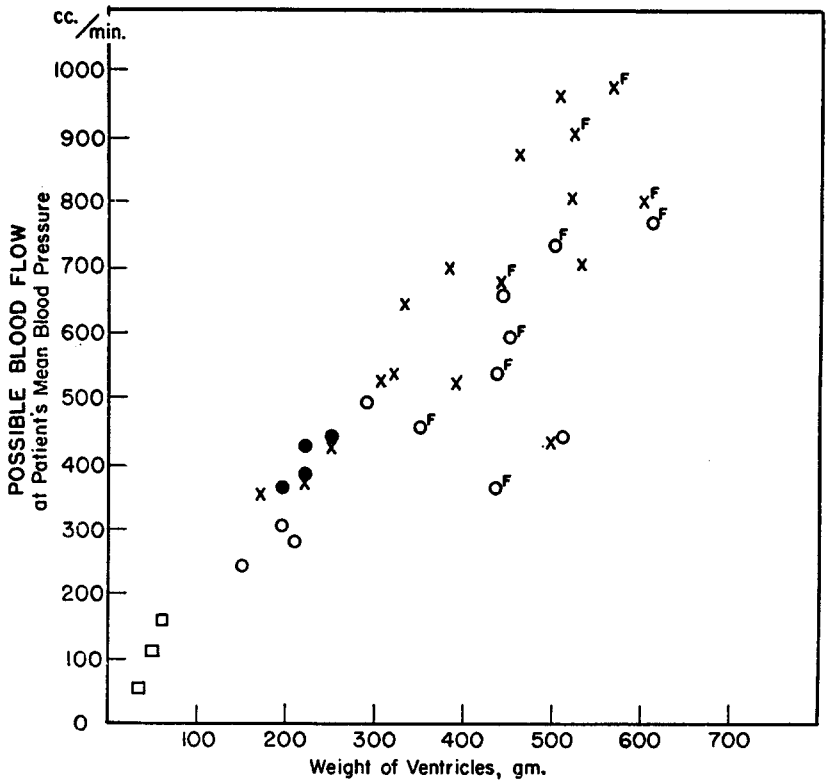

FIG. 3. "Possible blood flow," correcting perfusion rate at 100 mm. for patient's observed blood pressure (mean pressure taken as $S + D/2$), and for viscosity of whole blood compared with kerosene. □ = infants under 2½ years, ● = patients aged 25 to 40, × = patients 40 to 57, ○ = patients 60 to 84 years old. An *F* to the right of a case indicates congestive failure. While flow at a constant level of pressure, or even at patients' diastolic pressure, falls with increase in weight of ventricles, the flow at mean pressure existing during life remains fairly constant in many cases in spite of hypertrophy. The maximal flow at mean pressure is given by the formula $F = 2\ W + 50$, the minimal is $F = 0.9\ W + 30$.

average flow at 100 mm. Hg was 3.1 cc. per gm. per minute in those aged 25 to 40, 2.4 cc. in those 40 to 57, and 2. cc. in those 60 to 84 years old. There is a fall of 35 per cent in the average vascularity of hearts between the group 25 to 40 years and those over 60 years. This age difference is less striking with ventricular weight 260 to 400 grams, the average falling from 2.2 cc. in those 40 to 60 to 1.9 in those 60 to 78 years old, and there was no significant difference

between these age groups in hearts whose ventricles weighed over 400 grams. The age effect in normal organs is not peculiar to the heart, for kidneys of people in the age group 45 to 60 have a perfusibility 32 per cent less than those from people 18 to 32 years old, and diodrast clearances indicate a similar decrease in actual renal blood flow with age (1).

The most striking change occurs with normal growth, and with change in age from 2 years to 30. Here the decrease in perfusibility of normal hearts is nearly 50 per cent, and this can scarcely be regarded either as a pathological or involutional process. It shows that decrease in perfusibility with age or increase in bulk may be a normal adaptive process.

Hypertrophy.—The perfusibility of the heart decreases with hypertrophy. In the age group 40 to 60 the decrease is from 2.4 cc. per gm. per minute at weights under 250 gm., to 2.2 (−8 per cent) at weights of 250 to 400 gm., and to 1.5 (−37 per cent) at weights over 400. In the group over 60 years old, the decrease is from 2.0 cc. with less than 250 gm. of ventricle to 1.9 (−5 per cent) in those with 260 to 400 gm., and to 1.4 (−30 per cent) in those with over 400 gm. of ventricular muscle.

Congestive Failure.—There were four cases of aortic insufficiency in the group of heaviest hearts; two were rheumatic with hypertension and diastolic pressures of 80 mm. Hg. All of them had congestive failure, and two had coronary flows, calculated for their diastolic pressure levels, which were lower than any of the whole group, similarly reckoned. Otherwise there was no correlation, in a group of the same age and ventricular weight, between coronary flow and congestive failure (total eleven cases). Those dying of cerebral accident, prostatic disease, or other intercurrent illness had rates as low as or lower than any of the cases with congestive failure (Fig. 3). Nor did any of these nine cases show the fatty degeneration of the subendocardial fibers which is so characteristic of patients dying with severe coronary occlusion or acute or chronic anemia. In the latter group anoxia undoubtedly has been present for many hours before death, and is believed to be the cause of fatty degeneration. Such degeneration is rare in cardiac hypertrophy with no anemia or coronary disease.

DISCUSSION

As will be seen in Figs. 1 to 3 there is a great variation in coronary flow of hearts of the same weight, some of which is due to difference in age of the patient. The flow per gram of ventricular muscle, at the patient's mean or at his diastolic pressure, is much less variable over a wide range of heart weights than is the flow at a constant pressure level. Nevertheless age and hypertrophy do have a very striking effect in diminishing the capacity of the coronary bed. On the average a young adult with a normal heart has 2.4 times as wide a coronary bed as a man over 60 with a heart weighing 700 grams.

It is of course an everyday observation that young people with hyper-

thyroidism, hypertension, or healed valvular lesions are much less apt to decompensate than are those with similar, or milder, cardiac burdens at ages over 45. It is equally certain that cardiac hypertrophy is invariably present and often is marked in those who have had weeks or months of congestive heart failure before dying. Is it then proper to conclude that the diminished coronary bed, per gram of muscle, which occurs with age and with hypertrophy is the main cause or even an important cause of progressive myocardial failure?

There are several precedents for ascribing heart failure to myocardial ischemia. Harrison (7) inferred as much from looking at the heart fibers and calculating that oxygen could not diffuse into their depths, and Wearn reached that conclusion after finding few capillaries per gram (2). Kountz, who measured the coronary flow in revived human hearts (8), also felt that the flow was regularly diminished after failure and that this was an important element in causing failure. Since he did not perfuse all the hearts at constant pressure, but began at 20 mm. Hg and raised the pressure until dilatation set in, his published data do not prove that the coronary bed was narrowed, but only that the flow was poor at the levels of pressure which the muscle could maintain. In normal hearts he found the flow, at about 100 mm. Hg, ran as high as 1.5 cc. per gm. per minute and that histamine doubled the flow, thus reaching a level only a little below that found on perfusing hearts postmortem with kerosene, which is half as viscous as blood. Kountz' results give us further confidence in the value of our method, but neither they, nor the morphologic studies of Wearn or Harrison prove that myocardial ischemia is the main or most important cause of heart failure, nor do the observations here recorded necessarily establish such a relationship. It is evident that when calculated for possible blood flow at the patient's mean blood pressure there is an increase in flow, in the majority of hearts, proportional to the increase in weight. The vascular bed is therefore apparently adapted to supply a constant maximal volume at the existing pressure.

Against the view that hypertrophy leads to ischemia are several observations which pathologists have often confirmed. Failure may occur with heart weights from 400 to 1100 gm.; it may be absent in patients who die with hearts over 700 gm. in weight. There certainly is no specific fiber thickness or level of hypertrophy which can be stated to be incompatible with an active life, with considerable capacity for muscular effort and increased cardiac work. It therefore seems unlikely that there is any fiber thickness or level of hypertrophy at which the heart becomes unable to carry a basal load because of anoxia, and until it fails under a basal load there is no fatal outcome. In the second place the pathologist regularly finds specific changes, notably subendocardial fatty degeneration, in hearts of patients with hemoglobin levels below 25 per cent, whether this is due to bleeding peptic ulcer or any other cause. These changes are not found in hypertrophy and heart failure. It is probable

that the fall of 60 per cent in coronary capacity for flow, found in the man of 65 with a 700 gm. heart as compared with the man of 30 with a 250 gm. heart, is less serious in its effect than a fall of 60 per cent in hemoglobin, for the latter causes an increase in cardiac output and work of the heart. Ischemia in either case may contribute to or aggravate heart failure, but it cannot safely be regarded as the main or most important factor. In this series of cases the capacity of the coronary bed, at a constant level of pressure, was not less in those hearts which had manifested severe congestive failure than in the others, of the same weight, in which that phenomenon had not occurred, or was minimal and terminal.

It will be seen that the minimal rate of kerosene flow, calculated either at 100 mm. Hg or at the patient's diastolic pressure, does not fall below 1 cc. per gm. per minute, except in aortic insufficiency. If the correction for difference in viscosity which we found to apply in the kidney is used for the heart, this would imply that the capacity for flow of whole blood never falls below 0.7 cc. per gm. per minute. Even in the innermost fibers of the left ventricle, where only diastolic flow may be possible, this would leave a capacity for flow of about 0.4 cc. per gm. per minute, carrying oxygen at the rate of 0.08 cc. per gm. per minute. The basal O_2 uptake of the human heart can be estimated from that of the dog—it is probably of the order of 0.03 to 0.05 cc. per gm. per minute. These calculations of flow are based on observed rates, uncorrected for slowing due to the resistance in the perfusion system and are at least 25 per cent below the true rate for possible blood flow. Hence, using the lowest possible values, in the least vascular hearts without gross coronary disease, the margin of safety is well above what is needed. In the great bulk of muscle, where flow continues through systole, and in the average heart at its usual mean pressure, even with the most marked hypertrophy there remains a capacity for coronary flow three to seven times as great as needed to supply oxygen, and sufficient therefore to maintain a fairly high O_2 tension about the muscle fibers.

It is of interest that while myohemoglobin in the heart increases in animals exposed to low O_2 tension it does not increase with hypertrophy (2 *b*). Hence the theory that myocardial ischemia is invariably present in cardiac hypertrophy involves an unverified assumption not only that cardiac vascularity fails to adapt itself to tissue needs in the usual way, but also that the normal adaptation of myohemoglobin to oxygen tension is inhibited.

The calculations of Harrison, which he uses to support the theory that diffusion of O_2 cannot take place into fibers as thick as those of the hypertrophied heart, are based on the assumption that the heart contains no oxygen buffer and the muscle contains no blood during systole; that the venous O_2 level is usually as low as that he observed in one series of dogs and much lower than he himself has recorded in hearts of dogs under maximal loads; and finally

that O_2 diffusion into a muscle fiber can be calculated with the formula for diffusion from a single tube in the center of a cylinder of tissue. Actually one must use the formula for a cylinder bathed in fluid with the same O_2 tension as mixed venous blood, and assume that O_2 diffusion takes place all through the cycle, since the small vessels always contain red cells and the muscle contains myohemoglobin. The O_2 tension probably does not drop to 0 during systole even deep in the left ventricle. If it did the venous sample sould represent a mixture of entirely unsaturated blood from early diastole and highly saturated blood from the end of diastole, so that saturation of myohemoglobin and red cells in the capillaries would be very high at the onset of systole. Harrison himself noted coronary venous oxygen saturation of 40 to 50 per cent in hearts doing violent work, and equally high levels are found in the later, more extensive, and less indirect measurements of Visscher and of Gollwitzer-Meier. The possibility of high values is also indicated by these studies of the coronary bed.

If we use the formula of Hill (9, p. 60, *b*, i) for diffusion into a cylinder of tissue using oxygen at a constant rate, and accept 0.12 cc. O_2 per gm. per minute as the highest possible rate of human heart muscle metabolism, it appears that fibers up to 60 microns thick will be supplied with O_2 even at their very center. Oxygen utilization at 0.07 cc. per gm. per minute is about twice the basal level and a coronary flow of 0.6 cc. per gm. per minute is easily possible. This would result in a venous saturation of about 35 per cent and a fiber 90 microns thick would be fully oxygenated. Since 16 to 18 microns is about normal, and 40 microns rarely is reached in the most hypertrophied hearts, it seems unlikely that hearts with such coronary beds as those here reported, and with normal blood hemoglobin, ever suffer from failure of O_2 to reach the centers of fibers. This is in accordance with the observations on nuclei, which lie in the center of these fibers and appear to be quite normal even in the most massive hypertrophy. Anemia does lead to nuclear as well as sarcoplasmic degeneration.

The clinicians who have accepted myocardial ischemia following hypertrophy as the explanation of congestive failure are welcome to see in this study a functional confirmation of views based on morphologic evidence. Certainly a 58 per cent decrease in capacity for flow is more startling than a 40 per cent decrease in capillaries per c.mm. Most of this decrease was due to age alone; the greatest decrease in one age group was 37 per cent. It must be noted that the rates of flow in hypertrophy due to disease fall on precisely the same lines (Figs. 1 and 3) as those due to normal growth, and that a 46 per cent decrease in capacity for flow per gm. of heart occurs between infancy and the prime of life. Recalling how the vascular bed, even in the aged, hypertrophies to supply a tumor, or to provide collateral about an occluded vessel, others may be

dissatisfied with a theory of myocardial failure based on the assumption that the vascular bed of the heart cannot adapt itself fully to supply the needs of the muscle.

The pathologist or biologist perhaps can accept the thesis that the hypertrophied heart has a vascular bed ample for its needs, and that its fibers can be fully supplied with oxygen. They may not insist that the growth of the vascular bed exactly parallels an organ's increase in bulk. The pathologist may even be pleased that he need not explain to students why anoxia of heart muscle due to severe anemia or to coronary occlusion causes fatty degeneration, while the alleged anoxia of hypertrophy rarely does. Perhaps those of us who ascribe angina to myocardial ischemia will now find it easier to explain why angina is far less frequent with simple hypertrophy than with anemia and coronary disease. This may compensate for losing an explanation of myocardial failure which raised more questions than it answered.

SUMMARY

After eliminating vascular rigor, perfusing human hearts with kerosene under pressure postmortem gives values for coronary flow which seem an index of the maximum possible flow during life. This is 3.1 cc. per gm. per minute at 100 mm. Hg in normal men under 40. It is 35 per cent lower in the hearts of those 60 to 80 years old, and also falls in hypertrophied hearts. In old people it is 30 per cent lower in hearts over 600 gm. than in those under 350; in patients 40 to 60 years old it is 37 per cent less in hearts over 600 as compared with those under 350 gm.

In discussion it is brought out that while the decrease in coronary capacity associated with age or hypertrophy may play a part in predisposing some hearts to congestive failure, there is no evidence that the hypertrophied heart has an inadequate oxygen supply or that its fibers are too thick for adequate oxygen diffusion. Congestive failure cannot be ascribed to anoxia except in the presence of severe anemia, coronary occlusion, or tachycardia with low blood pressure. Decrease in perfusibility with age and growth may be a perfectly normal adaptation to the needs of the tissue; the perfusibility of the heart of the young adult is about half that of an infant at 2 years.

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