SPECIAL ARTICLE

Reactivity of Cardiac Vessels and Reparative Processes Following Cardiac Infarction

By Sergey V. Andreev, M.D.

Among various factors regulating the blood supply of tissues, the essential role belongs to the reactivity of blood vessels. Inadequate vascular reactivity, which is rarely observed in physiologic conditions, may occur rather frequently in pathologic situations. Inadequate and especially a distorted vascular reaction increases the circulatory derangement resulting in the delay of reparative processes. The changes in vascular reactivity are of great significance, mainly for the functioning of the heart.

In accordance with the above factors, there appears a very important assignment for the experimental investigations in the field of cardiovascular pathology, namely, for the studies of vascular reactivity in the heart and of different methods, which may lead to the activation of reparative processes following cardiac infarctions as well as of other organic impairments of the heart, which might become useful for the cardiologic clinic.

Materials and Methods

Vasomotor activity of the heart was studied with the aid of the motion picture, coronary onkography, and automatic registration of the amounts of nutrient fluid outflowing from the vessels of isolated heart.

A motion picture of the cardiac vessels was taken at the rate of 24 pictures per second in thoracotomized dogs exposed to the acute experiment and maintained under artificial respiration for a period ranging from 20 to 90 minutes. Films of the motion picture had registered the changes in form and size of the vessel lumina, occurring in the time interval of 0.04 second. Observations were made before and after the intravenous administration of various vascular substances; two drops of a 1 per cent solution of nitroglycerin were applied to the dog's tongue, while the physiologic saline was substituted in the control experiments. After completion of the acute experiment the motion picture films revealing changes in blood vessels were studied with the aid of a photomagnifier.

A special onkograph made of plastics or of thin aluminum measuring 0.6 by 1.0 to 1.0 by 1.5 cm. was arranged behind the middle third of the descending branch of the left coronary artery where its posterior surface is almost free of vascular outbranchings. The onkograph was connected by means of a rubber tube with a special recorder, which transferred all the alterations of nutrient fluid on kymograph.

Comparative onkography was performed in coronary, femoral, renal, and carotid arteries.

Control records of vascular oscillations in carotid, renal, and femoral arteries were made in dogs with normal respiration (without opening of the chest) following intravenous administration of physiologic saline instead of various vascular agents.

The hearts of adult human beings were also under observation. In one of the four experimental series we have studied the hearts of persons who died from a severe injury. Histologic investigations showed that in approximately one half of all these cases the coronary arteries revealed no alterations, whereas in the remaining half the coronary vessels were atherosclerotic. The second series of such experiments was conducted on the hearts of individuals who died from acute coronary insufficiency (stenocardia), and the third series on hearts with cardiac infarctions. The fourth series was done on hearts of human embryos and children of different age groups.

Two series of experiments were made on dogs: in animals with normal myocardium and in those...
with experimentally produced cardiac infarction, which was induced by ligation of the descending branch of the left coronary artery. The reactivity of the cardiac vessels in the second series of experiments on dogs was studied in different stages of developing cardiac infarction.

The pressure and temperature of a nutrient solution flowing through aortic cannula into the cardiac vessels remained constant during the entire experiment; therefore, the alterations in coronary outflow have been considered as an expression of oscillations taking place in vascular lumina and, consequently, in vascular tone.

Calculation of the nutrient fluid passing through the cardiac vessels was accomplished automatically by special equipment resembling that of Condon. The results of measurements were recorded on diagrams as curves showing the value of coronary outflow in milliliters per minute.

Bioelectric potentials from the superior vena cava of a man and from the heart muscles of a man and a dog were lead out through unpolarizing brush electrodes and were recorded in the stationary or portable electrocardiograph.

The dynamics of bioelectric potentials in the heart muscle were studied after the introduction of various vascular substances in the dog's body and in isolated human and animal hearts. The solutions of vascular agents were administered in the following concentrations: nitroglycerin, 1:210² to 1:3.10³; euphylarin, 1.5.10³ to 1:2.10³; k-strophanthins, 1.8.10⁴ to 1:10;²; adonizide and tincture of digitalis, 1:210² to 1:10.²

Activation of reparative processes in the heart muscle was studied in 129 adult albino rats and 109 rabbits. In the region of the middle third of the anterior ventricle wall, injury to myocardium was applied in all rats by a specially arranged eye-pincer. The area of the injured myocardial surface was 1.5 to 2.0 mm.²; its depth was 1.0 to 1.5 mm.

In 71 of the rabbits trauma to the heart muscle was also applied by means of the modified Koher's pincer. The injured area was 6 to 10 mm.²; its depth, 1.5 to 2.0 mm. In the remaining 38 rabbits, experimental cardiac infarction was produced by ligation of the descending branch of the left coronary artery in its upper third.

For evaluation of the functional state of myocardium the bioelectric potentials were studied in all animals as well as the histologic pattern of myocardial changes. One half of all the rats received vitamins and amino acids by subcutaneous injections, once every 2 days in the following doses: cobalamin, 10 to 30 μg.; methionine, 15 to 30 μg.; adenosinetriphosphate, 1.0 to 3.0 mg.; deoxyribose nucleic acid, 10 to 30 mg.; pyridoxine, 50 to 150 μg.; triptophane, 1.0 to 2.5 mg.

Results

Our observations have demonstrated that the tone of cardiac vessels may change in the form of rapid and, to some extent, independent, rhythmic oscillations or constrictions of the vascular wall. Simultaneously with frequent rhythmic constrictions of the vascular wall there is a manifestation of protracted changes in the general vascular tone, which may result in either contraction or dilatation. Both types of vasomotor activity may alter under the influence of various vascular substances. Depending on the type of vasomotor response, namely, whether it will be adequate or inadequate to the introduction of certain vascular substances, it is, to some extent, possible to characterize the functional state of vascular tone — its reactivity.

Independency of the rhythmic constrictions of the vascular wall is confirmed by the following factors: 1. During the restoration of cardiac activity there appears an intense and protracted (up to 2.5 hours) constriction of the superior vena cava in the human cadaver long before the onset of any contractile activity of the heart. Some time later the records of bioelectric potentials in human superior vena cava show arrhythmic constrictions (144 to 300 per minute) also in relation to the contractions of the heart. 2. As the cardiac function in man restores, the vasomotor activity in the heart may appear in the absence of and independently of myocardial contractions. 3. An amplitude of arterial oscillations does not always reflect the intensity of cardiac contractions and alterations in the level of the entire arterial pressure. 4. The form of oscillations in individual arteries may change independently of each other (for example, under the influence of caffeine, epinephrine, and amyl nitrite). 2, 5. 5. Periodic changes in width and length of cardiac arteries and arterioles, small veins and venules take place in time intervals of 0.04-0.06 to 0.8-0.12 second. These time intervals do not always coincide with the contractions of the heart muscle. 6. The peculiarities of vasomotor activity are characterized by the three types of rhythmic constrictions of vessels, which
differ from one another in amplitude, form, and frequency. Alterations of vascular tone are significantly obvious in type I and mildly obvious in type III. Type II occupies an intermediate position (fig. 1).

Arterial oscillations have a definite significance in the blood supply of the heart muscle. In type I, with a relatively greater amplitude of oscillations, the cardiac vessels are able to pass through themselves approximately twice as much nutrient fluid as in type III (224 ± 12 ml. and 109 ± 5 ml. respectively) and in type II (161 ± 8). Contractile function of the human heart muscle may be restored after death more frequently (in 45 cases of a total of 54) during the intense (types I and II) vasomotor activity.\textsuperscript{3, 4, 7, 8}

In some diseases and intoxications of the body (toxic dysentery, diphtheria, bronchopneumonia, acute stage of cardiac infarction) the vasomotor activity of the cardiac vessels is strikingly decreased and is very close to complete exhaustion. However, it increases in its intensity and appears as a compensatory factor, which enhances the blood supply of the heart in angina pectoris, in severe atherosclerosis, in hypertensive disease, and in the acute and subacute stages of cardiac infarction in man and in experimentally produced cardiac infarction in dogs.

Caffeine, amyl nitrite, nitroglycerin, adonizide, sodium nitrite, increpane, and especially strophanthin increase oscillations of cardiac vessels, whereas euphyllin decreases them. Epinephrine, against the background of a general elevation of arterial pressure, leads to a temporary decrease of oscillations, which remain on low levels for a few minutes.

Epinephrine inhibits the oscillations of the cardiac vessels, simultaneously increasing them in the peripheral arteries. This factor has to be taken into consideration for the evaluation of the role played by emotions in the blood supply of the myocardium, when epinephrine is discharged in increased amounts into the vascular bed.

The temperature of blood or of nutrient fluid averaging +37C. ± 1C. and the pres-
Rapid changes in the tone of cardiac vessels (designations on vertical and horizontal axes are the same as in figure 1). Thin, almost vertical, line indicates the rapid rise of vascular tone observed in experiment 134, under the influence of ephedrine solution (1:5:10). Thick line indicates the diminution of vascular tone following administration of nitroglycerin solution (1:3:10)3 in experiment 123.

Change of elevation of the vascular tone by its diminution, which may occur as a two-phased reaction (under the influence of intravenous administration of epinephrine) is sometimes observed in intact, healthy animals.2, 6, 10, 11, 12 Sometimes, in the physiologic condition, a two-phased vascular reaction may occur after introduction of several other substances (nitroglycerin, atropine, histamine, inerepane). The two-phased or distorted reaction of cardiac vessels in man was encountered in the acute stage of cardiac infarction, in stenocardia, in atherosclerosis, in hypertensive disease, and in the condition following craniocerebral injury and injury of somatic organs, which are followed by manifestations of traumatic shock, and in the first period of experiments with the restoration of human heart activity after death, when metabolic processes in heart muscle, according to the data of spectrographic investigations, were obviously impaired.13, 14

In the acute stage of cardiac infarction the vasodilating effect of nitroglycerin was observed in only one of eight experiments; in the remaining seven a two-phased or spasmodic reaction was present (fig. 3).

Human cardiac vessels being free of organic changes had shown in the majority of experiments an ability of dilating under the influence of ephedrine and nitroglycerin. Nitroglycerin and strophanthin caused more manifested dilatation of cardiac vessels, which were affected by atherosclerosis in comparison with the intact coronary arteries; ephyl-
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Figure 4
The effect of pharmacologic substances upon the human cardiac vessels following angina pectoris. Designations are the same as in figure 3.

lin, on the other hand, caused more intensive dilatation of the intact vessels.

Introduction of adoniside and digitalis had resulted in more intense constriction of atherosclerotic altered cardiac vessels in comparison with the intact ones. It is therefore evident that atherosclerotic coronary arteries of a man possess more manifested reactivity to vasodilating and vasoconstricting agents.

The tendency of the heart vessels to spasmodic reactions, despite the effect of euphyllin, was more frequently observed in conditions following craniocebral injury, traumatic shock, or after derangement in brain circulation (insult) appearing against the background of hypertensive disease. The same tendency had been demonstrated in approximately half of the experiments following hypertension (fig. 4).

The most constant spasmyotic effect upon the vessels of human heart in the acute stage of cardiac infarction and in conditions following acute coronary insufficiency (stenocardia) was observed after administration of euphyllin and strophanthin. Euphyllin possesses this quality even in the cases in which nitroglycerin causes spasmodic vascular reaction (fig. 5).

Spasmolytic effect was noted after administration of low concentration of euphyllin, nitroglycerin, and strophanthin, whereas high concentrations of these pharmacologic agents causes spasmodic reactions and seemed to be inadequate to the functional state of heart vessels in man during the acute stage of cardiac infarction and in conditions following acute coronary insufficiency. This phenomenon was also encountered in the acute stage of experimentally developing infarction in dogs.

In the acute stage of experimental infarction a spasmyotic effect has been revealed only in some individual cases, whereas in the remaining ones the spasmodic vascular reaction had predominated in the coronary arteries of dogs. Insufficiency of the vascular reaction in experimental cardiac infarction was demonstrated in the isolated heart as well as in the entire organism during investigations of bioelectric activity of the heart. (fig. 6).

Experiments on dogs have confirmed our observations concerning inadequate vascular response to the introduction of some vascular agents in the course of cardiac infarction in man.

Negative influence of focal impairments in the cardiac muscle upon the entire body and upon the reactivity of cardiac vessels...
brought about the necessity of experimental studies on the problems associated with the activation of reparative processes in the cardiac muscle.

The combination of vitamins used in our studies (cobalamine, pridoxine) and aminoacids (methionine, desoxyribonucleic acid, adenosinetriphosphate, and triptophane) was considered as a measure directed to the intensification of processes concerned with biosynthesis of proteins in the body, activation of transamination, transmethylation, phosphorylation, and transulfation. Thus, we intended to improve the reparative processes in the area of focal derangements and necroses in the heart.

The best results were obtained in the series of experiments on rats (with injury of the myocardium) and on rabbits (with cardiac infarctions) that received a complex treatment with cobalamine, methionin, adenosinetriphosphates, and desoxyribosenucleic acid. Normalization of the electrocardiogram in the hearts of animals so treated seemed to be faster than in the control animals (sixth to twenty-eighth day and fourteenth to forty-eighth day in rats and sixth to thirtieth and tenth to sixtieth day in rabbits, respectively).

In animals receiving the above treatment the disappearance of necrotic muscle fibers and the production of the mature connective tissue took place in a significantly shorter period. The development of connective tissue in the majority of these cases was limited to the areas of injury; furthermore, the nerves in such areas as well as in the regions of scar formation, showed no significant changes.

A complete healing of the cardiac muscle in control rats took place on the thirtieth to the fortieth day; in control rabbits, on the thirtieth to the sixtieth day, whereas in animals receiving complex treatment this happened much earlier (on the fifteenth to the twenty-fifth day in rats and on the twenty-fifth to the fortieth day in rabbits).8

Consequently, the treatment that we used (a combination of vitamins with aminoacids) in rats and rabbits having focal lesions of the heart showed a positive effect and had accelerated the reparative processes in the heart. This may have a practical significance in the clinic of internal medicine.

Discussion

Exclusively complex neurohumeral regulation of hemodynamics in man and in animals only allows to outline some of the mechanisms in the regulation of vascular tone.

I. P. Pavlov, studying neural mechanisms in the regulation of the vascular system, had stated that a significant role in this process...
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belongs to the chemical substances that are produced in the body. One of the principal problems of numerous investigators is to disclose the chief chemical processes that are essential in the impairments of vascular tone. Why does the vasomotor activity increase or decrease or, in some instances, completely disappear? Why do the changes in vascular tone lose their natural dynamics (replacement of elevating phase by the diminishing one) and become less mobile for a long time or reveal a tendency to spasmodic reactions?

One of the numerous causes leading to derangements in dynamics of vascular tone is hypercholesteremia and an increased synthesis of cholesterol and, apparently, of other vascular substances (epinephrine, norepinephrine) in the vascular wall. This was demonstrated recently with great conviction by many authors, who in their investigations used radioactive isotopes. 15, 18

Cholesterol enhances the tone of blood vessels, especially of arteries, and thus facilitates their transition into the spasmodic state. The impairment of phosphorylation, conditioned by deficiency of adenosinetriphosphate, which is characteristic of lesions appearing in the heart, may augment the sensitivity of vessels to spasmodic agents. In experiments with atherosclerosis the vessels of the rabbit’s ear respond more intensely to the vascular substances and reveal a tendency to spasmodic reactions.

Hypercholesteremia appears in a human body as a consequence of focal disturbances in the brain, hypertensive disease, atherosclerosis, intoxications, and avitaminosis. In the diseases mentioned above derangements in vascular tone were manifested by inadequate or distorted vascular reaction. The significance of the cholesterol dynamics in the blood for the reactivity of blood vessels confirmed by the fact that some substances (particularly, sodium fluoride), which reduces the amounts of cholesterol in the blood and causes the lowering of blood pressure, augments the effect of nitroglycerin upon the cardiovascular system during chronic experiments on animals; thus, the adequate reaction of vessels to the effect of nitroglycerin may be increased.

In atherosclerosis the synthesis of phospholipids and of cholesterol in the walls of the blood vessels significantly increases. Deficiency of pyridoxin and choline in the body may cause lipomatose infiltration of vessels.

When vascular tone is impaired (in hypertension) the content of thiamine in the blood falls significantly as well as that of ascorbic acid and carotin, although in the latter to a less extent. Deficiency of thiamine in the body predisposes the tissues of heart muscle and of blood vessels to the development of focal necroses.

The possibility of mutual transformation of cholesterol into sugar in the body is one of the indicators of close relations between the disturbances in cholesterol and carbohydrate metabolism. These predispositions are enhanced by the facts that a great number of patients with diabetes mellitus suffer from angina pectoris and that diabetic acidosis is often accompanied by the development of focal necroses in the myocardium.

Our knowledge of vascular tone is becoming more concrete. Vasomotor activity dependent upon the central nervous regulation and upon the function of numerous angioceptors, which are connected directly with the heart muscle by nerves, 19 could be as well defined by very complex synthetic processes taking place in the walls of the vessels and resulting in the production of various vasoactive substances.

Intoxication due to dysentery, diphtheria, or pneumococcal infection suppresses the vasomotor activity as a result of disturbances in general metabolism and, possibly, in the walls of blood vessels simultaneously with the functional and structural alterations in angioceptors. Focal derangements of vessels and of brain tissue in intracerebral hemorrhages, chronic irritation of the descending branch of the left coronary artery by a ligature in animals, cardiac infarctions in man and in experiments, and pathologic and experimental constriction of renal arteries
are followed by impairment of vascular tone (in a form of hypertension or hypotension) and of reactivity in the blood vessels up to complete distortion of vascular reaction. The reduction of vasomotor activity and distortion of vascular reaction may be encountered most often in an acute period of focal lesions; for instance, in the acute stage of cardiac infarction, when coronary blood supply may be diminished to 30 per cent. Focal lesions of the heart muscle also cause transformation of its vascular network.20, 21

Reflex influences, arising in the lesion and general toxic processes alter the metabolism in vascular walls provoking profound and protracted changes in vascular tone, which may be revealed in a form of hypertension or distorted reactivity of vessels.

Our experiments have demonstrated that the genesis of spasmic reaction of the cardiac vessels may be determined, not only by the atherosclerotic process, but also by a neurohumoral influence of necrotic focus upon the metabolism in the heart muscle and in the vascular walls as well.

Morphologic studies reveal zones of ischemia (arteriolospasm) around the necrotic focuses in the myocardium, e.g., the two-phased changes of vascular tone. Thus, functional and morphologic studies reveal the role of necrosis in the derangements of vascular tone. Atherosclerotic disturbances of metabolism in the vessels are accompanied by the augmentation of their reactivity, due to vascular agents, especially of the spasmotic type.

Besides the above-mentioned factors of metabolism (thiamine, pantothenic acid, adenosinetriphosphate, cholesterol, insulin, ipecac, epinephrine, magnesium, and potassium) other factors no doubt participate in the processes of regulation of vascular tone.

Focal lesions of the heart muscle, which cause profound derangements in metabolism of the heart, as well as of the entire body, require the application of adequate and complex treatment having a multilateral effect.

The complex treatment, which we used to accelerate the reparative processes in the heart muscle, is only a starting point in our studies in this direction.

Summary

It was stated that the human heart possesses a high vasomotor activity: in 1 to 3 minutes the coronary vessels may pass into a state of spasm or dilatation in such a manner that the volume flow may change up to 2 to 7 times. Apparently, this phenomenon discloses one of the mechanisms leading to prolonged spasm of the coronary arteries.

Vasomotor activity of the heart is characterized by three types of rhythmic oscillations of vessels, which differ from one another in amplitude, form, and frequency. In some intoxications (dysentery, diphtheria, pneumococcal infection) and diseases, vasomotor activity tends to decrease, whereas in the subacute stage of cardiac infarction in man and in dog, in angina pectoris, in atherosclerosis of the coronary vessels, and in hypertensive disease, it seems to be compensatorily augmented.

Two-phased or distorted reaction of heart vessels is determined not only by the atherosclerotic process but by neurohumoral influences of necrotic focus upon the metabolism in the heart and in the vascular wall.

The most constant spasmolytic effect upon the vessels of the human heart was obtained by the administration of euphyllin and strophanthin in low concentrations.

It was demonstrated that, in addition to vitamins, hormones, amino acids, and mineral salts, many other factors participate in the regulation of vascular tone.

Acceleration of reparative processes in experimentally produced focal lesions of the heart was encountered after application of a complex treatment on animals with vitamins and amino acids (B12, adenosinetriphosphate, methionine, and desoxyribonucleic acid).

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In the treatment of disease it was with Sydenham a cardinal principle to interfere as little as possible with the vis medicatrix naturae. He adopted as his own the fundamental concepts of Hippocrates, "Nature is the healer of diseases."—DAVID RIESMAN, M.D. Thomas Sydenham, Clinician, New York, Paul B. Hoeber, Inc., 1926, p. 36.
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SERGEY V. ANDREEV

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