IT HAS recently been reported that blood plasma from most species of mammals contains a protein system that causes a striking increase in the contractility of the isolated frog heart. The system is comprised of three globulins, called cardioglobulin A, B, and C. There appears to be a characteristic concentration of the cardioglobulins in the plasma of different species. It had been found in an earlier study, by a relatively crude assay technique, that the activity of the whole system in the plasma of patients with long-standing, severe hypertension was significantly greater than that for normal man or patients with other diseases.

The action on the isolated frog heart and the increased levels in hypertensive patients suggested that the system might have an important role in regulating the contractility of heart or blood vessels. This possibility is being explored by measuring cardioglobulin concentrations in various types of cardiovascular disease and by attempting physiological studies in experimental animals. The results of the former approach are reported in this paper. Although the evidence is circumstantial and a final decision must await direct demonstration in experimental animals, the data are consistent with the concept that the cardioglobulin system is essential for maintaining normal contractility of mammalian cardiac muscle.

I. CARDIOGLOBULIN IN HYPERDYNAMIC CARDIAC STATES

In considering the cause for the increased cardioglobulin activity in patients with long-standing hypertension, several possibilities were entertained. One was that the finding was incidental and had nothing directly to do with the abnormal cardiovascular state in these patients. A second possibility was that the normal function of cardioglobulin is to increase the tone of the smooth muscle of the arterioles and that the increased activity of the system in hypertensive patients represented a causative link in the chain of events leading to their disease. A third possibility was that cardioglobulin is a naturally occurring cardiotonic system in mammals, the presence of which makes for a certain level of cardiac contractility, and that the system is increased in response to the increased work done by the hypertensive heart.

Accordingly, it was decided to measure plasma concentrations of cardioglobulin not only in hypertension, but also in states characterized by increased cardiac work without increased arteriolar tone. Furthermore, since left ventricular stroke work is a product of the hydrostatic pressure developed by the ventricle and stroke volume, an attempt was made to evaluate these factors separately by investigating a group of patients with aortic stenosis (in whom left ventricular work is increased by virtue of an increase in left ventricular pressure) and also in a group of patients with aortic insufficiency (in whom left ventricular stroke work is increased because of an increased stroke volume without any significant increase in the isometric pressure developed by the ventricle).

Methods

Selection of Patients

In selecting patients for each group, an attempt was made to find cases in whom the severity of the basic lesion imposed a great additional load on the heart, but in whom significant cardiac failure had not yet supervened. Thus, in the hyper-
tensive group, the representative patient had hypertension of long standing with elevation of blood pressure persisting even after a period of bed rest in the hospital, significant cardiac enlargement and electrocardiographic evidence of left ventricular hypertrophy, but no cardiac failure. None of the eight patients in the hypertensive group took digitalis, with the exception of one person who had been digitalized for a period of three weeks before study because of a diastolic gallop and dyspnea on exertion without other symptoms or physical signs of cardiac failure. There was, of course, evidence of damage to other target organs in this group of patients, although only one patient had retinopathy more severe than grade 2. Renal functional impairment was found in seven patients, with significant azotemia in three. An attempt was made to assay plasma at a time when the patients were not receiving antihypertensive medication. Six of the group were not taking antihypertensive drugs at the time of assay, and the remaining two had significantly elevated blood pressure despite medication.

The patients with aortic stenosis likewise had histories of long standing, the severity of the narrowing being documented by pressure gradients across the aortic valve of at least 75 mm. Hg. Aortic stenosis was the sole lesion in seven of the eight patients, and was the only dynamically significant valve defect in the eighth patient. Cardiac enlargement, or at least electrocardiographic evidence of left ventricular hypertrophy, was the rule in this group. Cardiac failure was severe in two, present but readily controlled in two, and absent in the remaining patients.

With the exception of one patient whose valve defect had occurred as a result of an acute pneumoencephal encephalitis two years before observation, the patients with aortic insufficiency had histories of valvular disease dating back to childhood. The patients were all considered to have free aortic regurgitation and had been admitted to the hospital either for consideration of valve surgery or because of a clinical picture suggestive of subacute bacterial endocarditis or rheumatic activity. This group had also been selected with a view to finding patients with severe valve disease without a prominent degree of cardiac failure. Thus, none of the patients in this group had clinical evidence of edema either in the lungs or in the peripheral tissues, although two patients had lost weight on digitalis administered during a period of hospitalization. Despite the absence of definite signs of cardiac failure in most of the patients in this group, many of them, in the course of their long histories, had complained of weakness or dyspnea on exertion, and all of them were taking digitalis at the time of observation.

**Normal Controls**

A group of 12 normal controls was selected among employees at the National Institutes of Health. Both sexes and a broad age range were represented. No hypertension or other cardiovascular disease was known at the time of the study.

**Preparation of Human Plasma for Assay**

The collection of blood, preparation and storage of plasma, and assay of the samples are described in the accompanying paper on cardioglobulin assay methods. The present study was confined to the measurement of cardioglobulin C concentrations, since the measurement of cardioglobulin A is very difficult, and preliminary studies had shown that the increased plasma activity of hypertensives shown previously by a less refined assay method appeared to reflect an increase in cardioglobulin C more consistently than in cardioglobulin B.

**Results**

Table 1 shows the concentration of cardioglobulin C in the groups studied. It can be seen that both the hypertensives and the patients with aortic stenosis had concentrations of cardioglobulin C which were significantly greater than those of the normal controls. On the other hand, the concentration of cardioglobulin C in the plasma of the patients with aortic insufficiency did not differ significantly from that of the normals.

**Comment**

Each of the patient groups in this study is characterized by a particular type of hemodynamic picture. Thus, in the patients with essential hypertension, arteriolar tone, left ventricular pressure in systole, and left ventricular stroke work were all increased. In the patients with aortic stenosis, left ventricular pressure and stroke work were increased but arteriolar tone was normal. And in the patients with aortic insufficiency, left ventricular work was elevated, but approximately normal values of left ventricular pressure in systole and arteriolar tone were found. The two groups with high cardioglobulin C concentrations had in common increased left ventricular pressure and high left ventricular stroke work. The aortic insufficiency group, on the other hand, did not develop increased left ventricular pressure, and despite increased left ventricular stroke work, cardio-
globulin C concentration was normal. It appears, then, that cardioglobulin C concentration is in some way correlated with the development of left ventricular pressure in systole, and not simply with left ventricular work.

The data presented above are consistent with the view that cardioglobulin does not have to do directly with the regulation of arteriolar tone, but the system might enhance contractility of mammalian ventricular muscle, being increased in clinical conditions requiring the development of increased left ventricular isometric tension in systole.

II. CARDIOGLOBULIN C IN CONGESTIVE HEART FAILURE

If the cardioglobulin system were necessary for maintaining normal myocardial contractility in mammalian species, cardioglobulin deficiency could perhaps lead to decreased myocardial contractility and congestive heart failure. If such a syndrome existed, it would most likely be found among that rather small group of patients whose congestive heart failure cannot be explained, despite thorough clinical study. The conclusion of the clinician in such cases would be that cardiac failure is apparently due to a defect in contractility of the cardiac muscle, the nature of which cannot be determined by present diagnostic methods. Accordingly, a study of cardioglobulin C concentration in patients with cardiac failure was designed in which the patients were divided into two main categories: those in whom the failure appeared to be secondary to known valvular disease, and those in whom the failure appeared to be due to impaired contractility of the cardiac muscle.

Selection of Patients

The patients with cardiac failure secondary to valvular disease had mitral insufficiency (or, in two cases, aortic insufficiency) as the significant dynamic abnormality. Patients with aortic stenosis or hypertension were not included because of the findings noted in Part I of this study. Among the patients in whose disease of the myocardium appeared to be the primary cause of the cardiac failure, there were four patients, constituting a separate subgroup, whose myocardial defects had known bases, namely amyloid disease involving the heart, severe mumps myocarditis with fatal termination after a period of several months, recurrent rheumatic myocarditis, and extensive myocardial infarction. The remaining 17 patients with cardiac failure thought to be secondary to myocardial disease had no known etiological basis for their conditions. Although clinically this was a highly varied group with respect to age and severity of disease, the patients in it had in common the fact that the usual causes of cardiac failure—valvular disease, hypertension, myocardial infarction or atherosclerosis, pericarditis, myocarditis of known cause (or even myocarditis of unknown cause, the postulate of an inflammatory lesion perhaps being supported by fever or elevated sedimentation rate)—appeared not to be operative in this group of patients. Brief clinical histories of the patients in this group will be made available to interested readers on request.

Results

The results of this study are shown in figure 1, which is a scatter diagram in which cardioglobulin C concentration is plotted on the ordinate. In the first column are shown values for normal controls. In the second column are plotted concentrations of cardioglobulin C in patients with failure secondary to valvular disease. Those for the few patients studied with failure secondary to valvular disease. Those for the few patients studied with failure due to muscle disease of known cause are shown in the next column. It can be seen that the values of these two failure groups are scattered over a range comparable to that of the normal controls. The last column in the figure shows values for patients with idiopathic cardiac failure. The striking result is that, in contrast with the previous groups, the distribution of points in the last column appears to be bimodal. Nine of the 17 plasmas have concentrations much lower than in any other group,
whereas the other eight patients with idiopathic failure have values which are distributed in the normal range. In other words, the idiopathic-failure patients can be divided into two populations, one group having normal cardioglobulin C concentrations, the other having extremely low values.

**Comment**

The severity of the cardiac failure was, on the average, comparable in the various groups studied. Comparison of the valvular disease group with the normal controls suggests that failure per se is not associated with any great reduction in the concentration of cardioglobulin C. The results of the assay of the patients with idiopathic heart-muscle disease indicate that in this group there was a population with unusually low concentrations of cardioglobulin C. These patients could not be distinguished clinically from the ones with normal cardioglobulin concentrations. Within the framework of the hypothesis under consideration, the results are consistent with the idea that among patients with idiopathic cardiac-muscle disease, there are some who have a primary deficiency of cardioglobulin which, perhaps, leads to the development of cardiac failure.

**Discussion**

The question under consideration in the studies reported in this paper is: Does the plasma cardioglobulin system have anything to do with the mammalian heart? Indeed, the system was named "cardioglobulin" only after the conclusion of these studies, although the results do not provide any direct evidence that allows an unequivocal affirmative answer to the question posed. However, it is clear from the first part of this paper that the concentration of cardioglobulin C is increased in two clinically unrelated conditions, essential hypertension and aortic valvular stenosis, which share a common pathological physiology only insofar as the left ventricle is concerned. Since both conditions are characterized by increased plasma concentrations of cardioglobulin C, it is difficult to avoid the conclusion that events occurring within the left ventricle and the plasma concentration of cardioglobulin C are in some way related. The normal concentrations found in patients with aortic insufficiency suggest that the intraventricular event involved is not the performance of stroke work per se, which is increased in all three of the conditions under consideration, but is more likely to be the development of isometric tension in systole, which is not increased in aortic insufficiency as it is in hypertension and in aortic valvular stenosis. These observations bring to mind the fact that when stroke work is increased, the response of the heart with respect to oxygen consumption is different, depending on whether stroke volume or output pressure is the variable causing the change in work. Thus, oxygen consumption changes very little when stroke volume is increased, but becomes much greater when aortic pressure is raised.

In view of the findings in aortic stenosis and hypertension and the known cardiac action of cardioglobulin on the frog heart, it is reasonable to postulate that cardioglobulin enhances the contractility of the mammalian heart, and that there is a compensatory in-
crease in the clinical conditions characterized by the development of increased left ventricular pressure in systole.

To state that this is only a hypothesis with little supporting evidence at the present time is certainly unnecessary for the critical reader. The hypothesis did, however, provide the conceptual framework for the study on cardiac failure. Here the result was that, whereas congestive failure caused by valvular disease is not associated with decreased concentrations of cardioglobulin C, there was a group of patients with unexplained failure in whom plasma cardioglobulin concentration was diminished. A primary deficiency of cardioglobulin might have led to the congestive heart failure in these patients. That the deficiency may have been in some way secondary to the myocardial disease in this group cannot, of course, be ruled out at the present time.

Since only a small number of plasma assays, perhaps three or four, can conveniently be performed in one day in our laboratory, it has not been possible to answer many questions that arise in connection with the studies reported. What, for example, is the effect of digitalization on the plasma concentration of cardioglobulin? Preliminary results in a small number of patients indicate that cardioglobulin C concentration is not affected by digitalization of the patient. The effects of antihypertensive agents or of successful surgical correction of aortic stenosis have yet to be determined. Likewise, the concentration of plasma cardioglobulin in patients with increased right ventricular pressure or with other types of cardiac abnormality are subjects for future investigation.

One may also ask whether all three components of the cardioglobulin system vary together in the same direction in various clinical conditions. This point has not yet been studied systematically, but preliminary indications are that the kind of correlation made for cardioglobulin C probably does not exist for cardioglobulin B. The A component would appear, in the few plasmas studied (see table 1 and reference 3), to vary in relation to cardioglobulin C. Such findings might be expected in view of the action of the system on the isolated frog heart. Cardioglobulin B becomes bound to the heart, cannot be washed away subsequently, and is not altered in activity by interaction with the other components of the system. In contrast, the interaction of the three components to cause increased contractility of the frog heart is associated with a rather rapid decrease in the biological activity of cardioglobulin A and C. If similar events occur in the mammalian organism, one might expect that cardioglobulin A and C are in a rather dynamic state, the plasma concentration reflecting utilization at the cardiac surface and production by an as yet unknown site.

Summary

The plasma concentration of cardioglobulin C has been compared in hypertension, aortic stenosis, aortic insufficiency, and in a group of normal subjects. The concentration in subjects with aortic insufficiency was normal; whereas in the groups with aortic stenosis and with hypertension, the concentration was significantly increased. These findings suggest that there may be some relationship between the increased plasma concentration of cardioglobulin C and the development of increased left ventricular isometric tension in systole, which is characteristic of patients with aortic stenosis or essential hypertension.

Cardioglobulin C concentration was measured in a group of patients with congestive heart failure secondary to valvular disease, and in two groups of patients with cardiac failure secondary to myocardial disease, either of known or of unknown cause. The results showed that the cardioglobulin C concentration in congestive failure secondary to valvular disease or to muscle disease of known cause was not significantly different from normal. The 17 patients with congestive failure secondary to muscle disease of unknown cause could be divided into two populations with respect to cardioglobulin C concentration. One group had concentrations which fell in the normal range, whereas the other group had extremely low values. The findings are
discussed in relation to the hypothesis that the cardioglobulin system may be essential for maintaining normal myocardial contractility in warm-blooded animals.

Acknowledgment
This study could not have been done without the enthusiastic cooperation of many physicians in the Washington, D. C. area who enabled us to study their patients. We should like to express our great appreciation for the help we received from members of the surgical and medical staffs of the National Heart Institute, Georgetown University Hospital, Mt. Alto V. A. Hospital, D. C. General Hospital, Naval Medical Center, Walter Reed Hospital, and the Washington Hospital Center.

References

BOOK REVIEWS


Portions of this book are concerned with trigonometry and spherical geometry. There are some interesting three-dimensional representations on the flat page. For instance, figure 1 incorporates the three scalar leads X, Y, and Z; the three planar projections, frontal, horizontal, and sagittal; and the three-dimensional spatial loop, all in the same two-dimensional drawing. The author's aim is to achieve precision and orthogonality which is a very desirable goal in vectorcardiography. However, after an auspicious beginning, we find that the author reverts to the well-known QRS-T angle, as derived from the 12 conventional leads ordinarily used in electrocardiography. It seems to the reviewer a little incongruous to use the sophisticated methods introduced in this book to analyze relatively nonprecise, nonorthogonal source material such as the 12 conventional scalar leads. The author also leans somewhat on the ventricular gradient, which is a concept whose significance has been much disputed. In brief, the book, in parts, is an interesting and stimulating one to read.


This year marks the appearance of revisions of several standard textbooks. The seventh revision, of what many students have been referring to for almost a quarter of a century as "Best and Taylor," has been revised with the help of several collaborators.

The name of the author of the cardiovascular chapters automatically prompted the reviewer to turn to the chapter on the coronary circulation. This reviewer is pleased with this chapter, as well as the others. The use of arrows to indicate directional changes in cardiovascular function to stress states (page 328) was rather unusual for the author to use, because characteristically the author has always attempted to express function in a quantitative way. The use of arrows is understandable, because the available information on stress situation is far from complete. As in other textbooks, one cannot help but wish that for the sake of circulation research more space should be devoted to cardiovascular physiology.
Cardioglobulin: Clinical Correlations
EDWARD LEONARD and STEPHEN HAJDU

_Circ Res._ 1961;9:891-896
doi: 10.1161/01.RES.9.4.891

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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