PHARMACOLOGY *of the* FAILING HUMAN HEART

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BLACKWELL
SCIENTIFIC PUBLICATIONS
OXFORD

Published simultaneously in the United States of America by Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Illinois.

Published simultaneously in Canada by The Ryerson Press, Queen Street West, Toronto 2.

First printed, December, 1950

Printed in Great Britain for BLACKWELL SCIENTIFIC PUBLICATIONS, LTD.
by A. R. MOWBRAY & CO. LIMITED, London and Oxford

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PREFACE

THE development of the intracardiac catheter as a physiological instrument applicable to man has opened up a vast new field of research on the problem of the failing human heart. The heart can be approached directly and its output and haemodynamic behaviour are now subject to more direct observation than ever before. Some older ill-defined concepts of heart failure have been consolidated and many have been discarded as a result of the newer observations. In the Post-graduate Medical School of London, during the past eight years, we have made a systematic study of patients with various forms of heart failure with these new techniques. From time to time we have ventured to report on our findings, but the growth of experience with the technique in our own School and elsewhere has made many of our earlier ideas seem over-simple. We should emulate Fuller Allbright and say that 'any hypothesis propounded is liable to change without notice'. Working hypotheses are made on the basis of known facts and the application of current physiological opinion, but the inexorable development of fresh factual observation and altering conceptions compel parallel changes in outlook. The view previously expressed that primary venous pressure reduction might be largely responsible for determining success or failure of digitalis therapy is no longer acceptable. One attraction of this hypothesis was that it afforded a possible explanation of therapeutic successes and failures: but mere usefulness is no substitute for accuracy and the whole problem is once again in the melting pot. Observation is more important than interpretation: while hypotheses may be lost, factual observations have been gained and extended and technical progress in more accurate recording of intracardiac pressures has now been added. I welcome the invitation of the editors to review the present situation in the light of the new knowledge which is now available.

There is no doubt that in the early days of cardiac catheterization most workers were over-impressed by small changes in output which can now be regarded as devoid of statistical significance. With the use of a somewhat bold technique there was too great a desire to use *all* the available figures and draw whatever conclusions seemed possible. Now that the safety of the procedure has been established and widely accepted we realize from a much wider experience that earlier deductions were being made from too small numbers of observations. A much more critical approach is necessary. Greater numbers of observations will be necessary before many of the outstanding problems can be seen in proper perspective.

The work here reported could never have been done without the loyal co-operation of the department staff and research assistants. I wish to mention particularly Professor E. P. Sharpey-Schafer, Dr. S. Howarth, Dr. Paul Wood, and more recent workers, Drs. Ahmed, Bayliss, Kelly, Reid, Etheridge, and Hyman. Personal contact and free discussion and criticism with Drs. André Cournand, Dickinson Richards, Eugene Stead, J. V. Warren, J. Lenègre, and Lars Werkö have helped to mould the opinions expressed. Professors Lenègre and Loubatières kindly put some unpublished data at my disposal.

It is appropriate that this short monograph should be published in the American Lecture Series. The research material has been presented in lectures in various parts of the United States, and I specially wish to acknowledge the honour of giving the following lectures:

Henry Jackson Lecture to the New England Heart Association, 1947.

Guest Lectures to the California Heart Association, 1948.

John H. Musser Lecture in Tulane University, New Orleans, 1948.

Thayer Lectures, Johns Hopkins Hospital, Baltimore, 1948.

J. McM.

London, 1950

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CHAPTER I

GENERAL IDEAS ON HEART FAILURE

THE idea of depression of cardiac output as a necessary consequence of organic heart disease was courageously banished by Harrison[1] some fifteen years ago. He was willing to accept the evidence, based at that time on somewhat indirect methods of estimation of cardiac output in man, that the output of the heart need not necessarily be low in patients with heart disease even in heart failure. Catheter studies have now established quite clearly that certain types of heart failure may even be associated with a resting cardiac output above the normal level which in a placid, recumbent adult averages about 5·3 litres per minute. Heart failure from the haemodynamic point of view may thus be subdivided into low output and high output types.[2, 3]

In the low output group we find those which are the result of intrinsic heart disease such as valvular and ischaemic disease. Hypertensive heart disease also falls into the same category, apparently the mechanical overburdening of the heart by increased arterial resistance plays a part in the production of an ultimate cardiac breakdown of the same type as that seen when the cardiac embarrassment has resulted from distorted or leaking valves.

By contrast the high output type of cardiac failure takes place in conditions which call in the first instance for an increased cardiac output. Such states include:

1. Severe anaemia.
2. Beri-beri.
3. Emphysema.

4. Mechanical overloading of the circulation:
   (*a*) arteriovenous aneurysms;
   (*b*) widespread Paget's disease of bone.

It will be understood that anaemia and emphysema are, for different reasons, accompanied by decreased oxygen-carrying power of the blood, and adequate tissue oxygenation may only be achieved by a more rapid circulation. In the group 4 of the above conditions the circulation is encumbered by an additional 'parasitic' circulation which, by producing a long-term embarrassment, may ultimately lead to failure. All the manifestations which the clinician recognizes as heart failure may appear in this 'high output group'—particularly venous congestion, peripheral oedema, and dyspnoea. The two groups of heart failure may be differentiated clinically, as patients with the high output variety usually have warm extremities and full or bounding peripheral pulses. The extrinsic cause of circulatory embarrassment, e.g. anaemia or emphysema, is usually recognizable. The practical importance of recognition of the two groups is that treatment is different. It should be directed to the cause of the failure in the high output types.

When the output of the heart has fallen to a low level in heart failure the clinical picture is different. The extremities tend to be cold and blue and the peripheral pulse small. Occasionally *in extremis* the nose and finger-tips may become cyanotic or even black: central veins like the jugular are engorged while peripheral veins like those at the elbow may contract down to mere threads.

While the sub-division of cardiac failure into these two contrasting haemodynamic types may often be clearly recognizable, it should also be realized that they are not completely and sharply demarcated in all instances.[3] It should be kept in mind that in the more advanced stages of emphysema heart failure, for example, the cardiac output may sometimes be observed to fall below the normal value.[4] It might be thought that thyrotoxicosis would fall into this high output group, but, in our experience, when thyrotoxicosis is accompanied by gross venous congestion

and oedema the output has been low.[5] Experience of this type of failure is limited nowadays by the efficiency of modern anti-thyroid remedies. In the earlier stages of thyrotoxicosis, however, the cardiac output, as expected, is well above normal. Early manifestations of cardiac failure may make their appearance in the 'low output' group before the resting output has fallen very much and even while the output is still within normal limits. This applies particularly to patients who develop left ventricular failure as a result of hypertensive or aortic valve disease. In such patients attacks of dyspnoea and pulmonary oedema occur while the output of the heart is normal or even slightly above the normal average. We may imagine that the relatively efficient right heart is driving the enfeebled left ventricle, but the output of the latter is only maintained at the expense of extreme pulmonary vascular engorgement which results in breathlessness.

Depression of the resting cardiac output is therefore absent in the early stages of most forms of heart failure, and significant diminution of cardiac output is only seen in the late stages. It is obvious, however, that in all conditions leading to failure the heart is *under load* and its capacity to sustain extra work is decreased. It is difficult to define heart failure except in some such terms as follows: *the heart is failing when its capacity to increase output is seriously impaired and when output is only maintained at the expense of a raised venous-filling pressure; the late stages are characterized by an output which is falling below the previous level, with further increase in systemic venous congestion.*

The mechanism by which the venous pressure rise takes place is a matter of some interest.[6] It is clearly not a simple back pressure effect, at least in the early stages of cardiac failure, as significant rises in venous pressure are found when the output of the heart is normal or high. Under these circumstances blood is not accumulating on the venous side of the circulation from failure of the heart to transfer blood into the arteries. An alternative explanation seems to be that physiological mechanisms for the maintenance of an adequate cardiac output come into action and among these adaptations we must postulate a veno-

motor mechanism which raises the venous pressure sufficiently high maintain to the output of the heart at the required level (Fig. 1).

It seems likely that the early rises of venous pressure take place first on exercise. It has been shown that sustained rises of venous pressure following exercise only occur in cardiac patients.[7] In normal subjects the rise in venous pressure in exercise is small and is very quickly restored to normal immediately the exercise ceases.[6, 8] The raised venous pressure of exercise becomes sustained as the diseased heart fails to recover from the strain. The beneficial effects of rest in the early stages of heart failure are in keeping with this conception.

Although we shall have little more to say about physical rest as a therapeutic remedy in cardiac failure, it is probably as important in the régime and management as all the other remedies put together. Early warnings of failure, such as nocturnal dyspnoea and inability to walk up hills, may in certain instances be very considerably alleviated if the patient can spend his weekends in bed. When physical rest to the heart is being considered it is well to remember that the resting output of a normal individual is lower during quiet standing than in complete recumbency.[9] As the patient with nocturnal orthopnoea knows, the optimum position to relieve his heart is sitting on the side of his bed. Rest to the heart at certain critical stages of heart failure is best provided when the patient is propped up or sitting up in a cardiac bed or a high armchair.

In addition to the above types of heart failure which are characterized by an overload effect created either by extrinsic factors or intrinsic abnormalities of a *chronic* variety in the valves of the heart or the myocardium, there are other types of heart failure which may result mainly from some more acute intrinsic disease of the heart muscle. These include diphtheritic and rheumatic myocarditis. At the acute phase of such diseases the general trend of opinion is that relatively little may be expected in the way of therapeutic effects from the remedies applicable to more chronic types. The failure which accompanies these special varieties of heart disease has not yet been studied from the

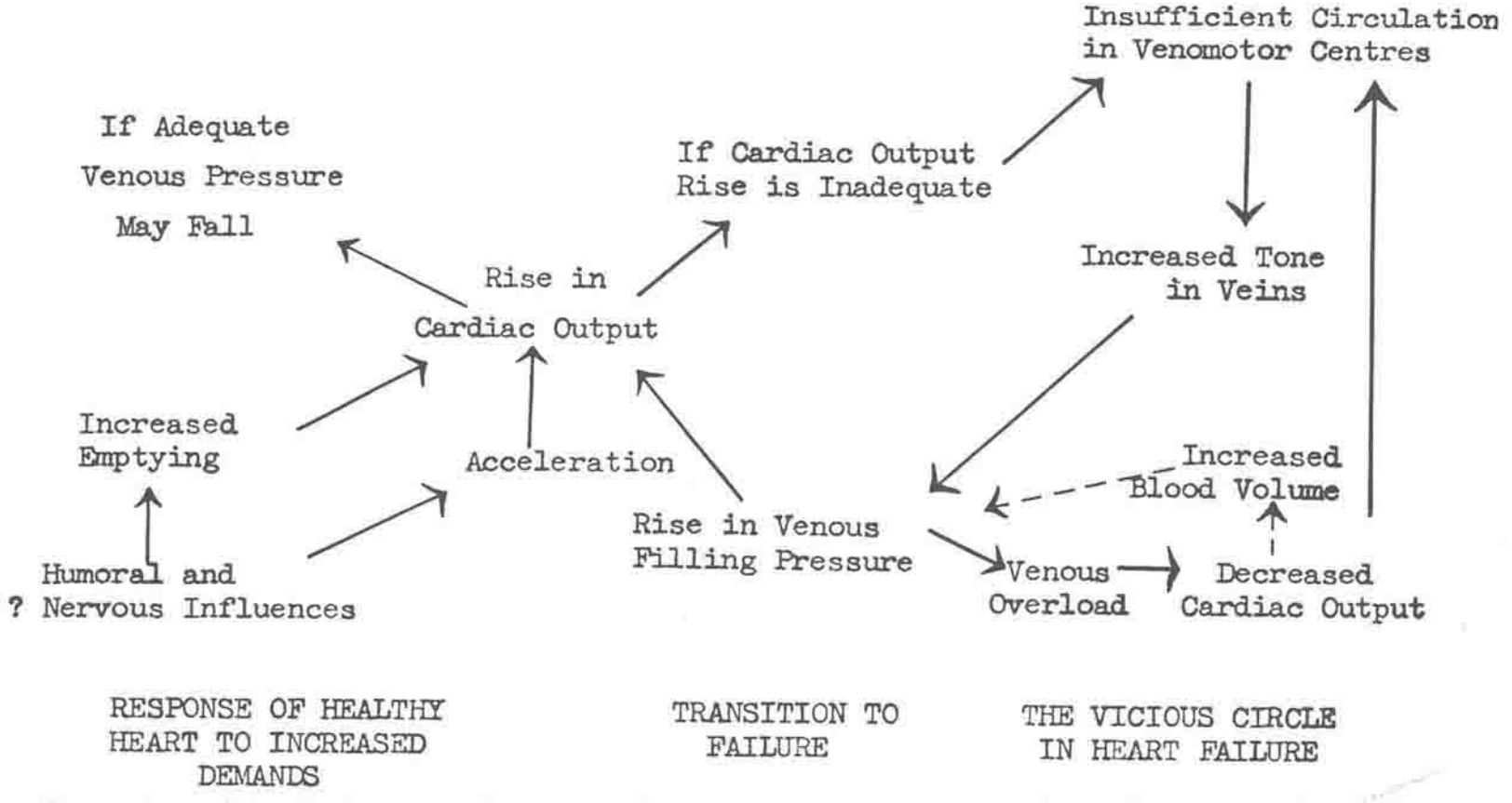

FIG. 1. The relationship between cardiac output and venous pressure in health and in heart failure. A rise of venous pressure does not play much part in increasing the cardiac output in normal subjects until exercise becomes exhausting. This stage is reached more readily in the presence of heart disease, and it is possible that a vicious circle may be created in the advanced stages of cardiac failure, i.e. inadequate cardiac output induces reflexly a rise in venous pressure, but this may overstretch and overload the heart, leading to further failure. (Reproduced from the *American Journal of Medicine*.)

haemodynamic and pharmacological point of view with the newer techniques.

It is important, however, to keep the myocardium strongly in mind throughout our therapeutic approach to cardiac patients. It is only in the immediate responsiveness and ultimate adaptability of the myocardium that our hopes lie for any amelioration in the course of most forms of organic heart disease. The following common types of clinical experience may illustrate the meaning. Manifestations of cardiac failure with pulmonary and systemic venous congestion may appear during the course of acute myocardial infarction. With rest and care these may ultimately clear up and the patient return to useful life for a period of years. The anatomical basis of this recovery is probably 'physiological' hypertrophy of the remaining myocardial fibres. Less dramatically, one may encounter patients with calcified aortic valves or narrow mitral valves who have lived into the sixth and seventh decade before cardiac failure becomes manifest. In many instances we have evidence that the anatomical embarrassment has been present for, perhaps, twenty years, and yet the process of adaptation seems to be complete and compatible with sedentary or moderate work over this long period. Conversely, in those patients with rheumatic heart disease who go rapidly downhill with a progressively severe disablement over a period of five to ten years, post-mortem examination frequently reveals smouldering rheumatic carditis. Similarly, it seems clear that heart failure in thyrotoxicosis is not entirely the result of prolonged tachycardia in such patients but is rather a consequence of some metabolic disturbance in myocardial contractility. It is also a matter for speculation why the heart breaks down ultimately in patients with hypertension. Chronic benign essential hypertension may be well tolerated for decades, and then, without further apparent rise in the systemic arterial pressure, heart failure suddenly supervenes. Myocardial factors in such patients have not yet been convincingly demonstrated anatomically, but there can be little doubt that some other critical event

has occurred turning a simple physiological compensatory hypertrophy into an enlarged dilated failing heart.

Finally, we should emphasize a difference in adaptation to two types of overload. It was shown experimentally by Müller[10] that the isolated mammalian heart could tolerate an increased work load created by a raised minute volume very much better than a similar work load imposed by increased arterial pressure. The normal heart can probably adapt very readily to a demand for increased output up to five times or more the resting normal value. If, however, the output remains constant but the arterial pressure is increased acutely, doubling or trebling the arterial pressure will at once lead to failure. These points may be illustrated again from clinical experience. An acute rise of arterial pressure occurring, for example, in acute nephritis, may be associated with dyspnoea and failure, although the pressure rise is quite a modest one. Conversely, patients with traumatic arterio-venous aneurysms may tolerate large increases of resting cardiac output through many decades. The author has observed one patient who had a femoral arterio-venous communication following a gunshot wound in 1918. He was capable of active work and considerable activity until 1947, when he alarmed his physician by developing auricular fibrillation. At this stage cardiac catheterization was done; there was no venous congestion but the resting cardiac output was 12·1 litres per minute. The patient had apparently tolerated an increased resting output of this order for over thirty years, and in spite of the coincidence of auricular fibrillation did not, even then, develop any manifestations of cardiac embarrassment. A somewhat similar state of affairs is seen in atrial septal defects. In this condition a large volume of blood poured through from the left auricle to the right may be added to the blood returning to the heart via the systemic circulation. The resting output of the right ventricle in such patients may be raised perhaps as high as three times the normal.[11] Yet these subjects are often capable of leading active lives. I have known a young man with this condition who played strenuous football once a week. Increased output then is much less likely

to strain the heart, and it is a less important factor in determining failure than an increased peripheral vascular resistance.

Responses to drugs and other methods of treatment in cardiac failure vary with the differing aetiological varieties of the syndrome. Not only may the response vary from one aetiological group to another, but it may also be dependent upon the stage of failure and perhaps to some extent on the speed of development of cardiac failure in any single aetiological group. Hearts which have ceased to make any response to members of the digitalis series may respond, albeit temporarily, to the administration of theophylline-ethylene-diamine.

CHAPTER II

THE BEHAVIOUR OF THE FAILING HEART: RESPONSES TO VENESECTION AND MERCURIAL DIURETICS

STARLING'S law of the heart. Just before the first World War, Starling studied the factors regulating the output of the isolated mammalian heart. He established what was called the Law of the Heart, which indicated that the output of the heart was determined by the diastolic fibre length.[12] The longer the myocardial fibres, within physiological limits, the greater the contractile response. With a greater inflow of blood into the isolated heart during diastole the fibres of the heart chambers were stretched and the output per beat was correspondingly increased. The venous inflow in turn was largely dependent upon the venous filling pressure. From the data he obtained Starling was therefore able to show a fairly direct linear relationship between venous filling pressure and cardiac output (Fig. 2). There was, however, a little doubt about the exact part played by the pressure factor itself in determining fibre length. Starling himself concluded that diastolic tension within the ventricle was not the deciding factor, but the optical methods of registering diastolic pressures which Starling used were later subjected to criticism by Wiggers. Wiggers concluded that strength of the ventricular beat was dependent on very small changes in diastolic tension, the recognition of which was not possible by the methods which Starling had used.[13] Wiggers' investigation seemed to establish the influence of filling pressure in determining the output of the heart. In recent years the general applicability of Starling's Law to the mammalian heart *in situ* has been called in question, and from the work of Warren and Stead[14] it is quite clear that Starling's Law no longer holds the dominant position in physiological

integration of the circulation once ascribed to it. The output of the normal heart is certainly subject to nervous and hormonal

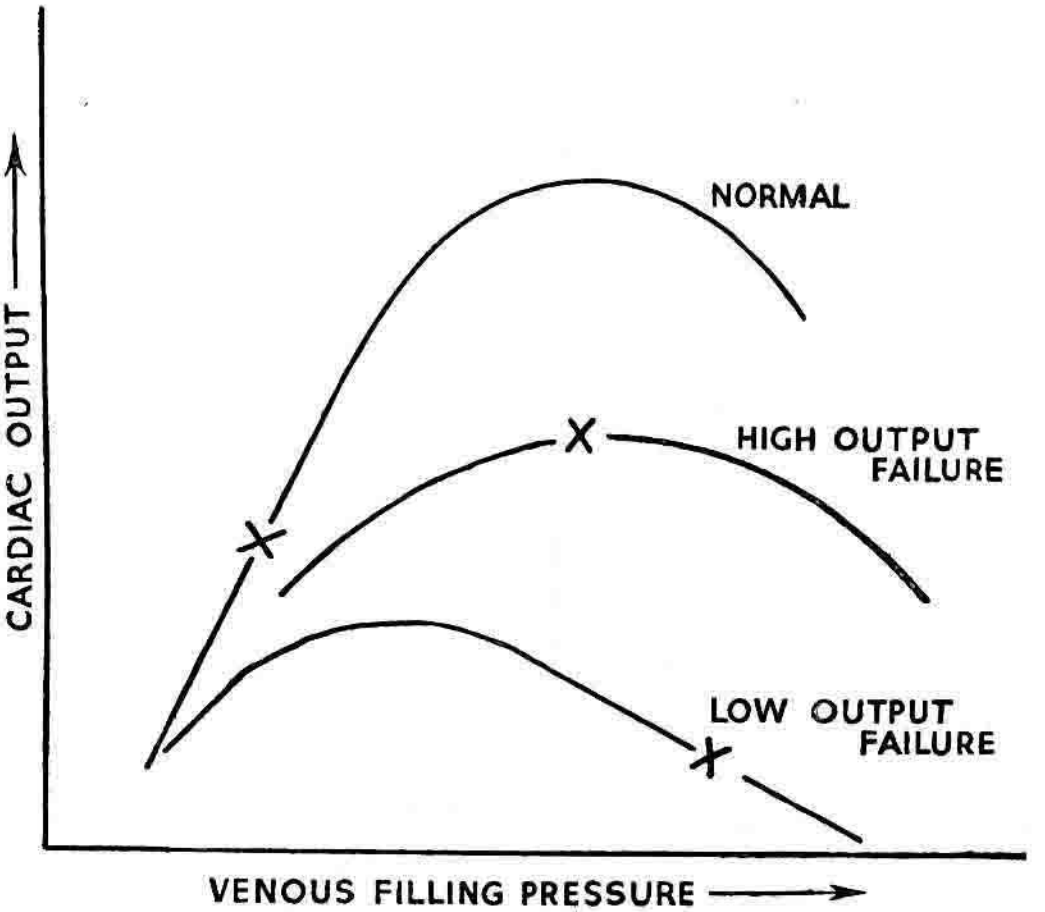

FIG. 2. Hypothetical Starling curves in normals, high output failure and low output failure. The normal heart may increase its output to a high level with increased venous filling pressure. In anaemic heart failure the high output is probably maintained at least in part by an increased filling pressure. Further increase of this filling pressure may lead to a decrease in output. In severe low output heart failure the heart has in most instances passed to a stage at which increments of pressure lead to decreases in cardiac output. The response is usually a fall in output with increased venous return and, conversely, venesection may lead to improvement in output. (Reproduced from *Clinical Science*.)

control and regulation. The influence of venous filling pressure may only play a small and rather subsidiary part in the regulation of cardiac output within the physiological range in normal intact man.

There are, none the less, many circumstances in which the