Starling and the Concept of Heart Failure

By SIR GEORGE PICKERING, M.A., M.D., F.R.C.P.

ERNEST HENRY STARLING has probably contributed more than any man to our understanding of heart failure. Thus his early experiments on edema formation and his assessment of the factors concerned have formed the basis for all subsequent work on this subject. His work with Patterson and Piper\(^1\)\(^,\)\(^2\) on the mechanical factors involved in the response of the heart to changes in load have formed the basis for our understanding of how the heart’s work as a pump is adjusted to the varying demands made upon it, and have incidentally provided the key to our understanding of heart failure as seen in man. Nevertheless, in the course of time what Starling and his colleagues actually observed, and what they deduced from these observations that was relevant to heart failure, have become somewhat obscured. And since it would seem to the writer that Starling’s concept of the nature of heart failure was closely in accord with what actually happens in man, it seems right to present some extracts from the original papers so that cardiologists, whether practitioners or investigators, may be more fully informed than they are.

It is to be remembered that Starling was a physiologist, and that though undoubtedly he received much inspiration from human disease, he was more interested in basic mechanism than in the interpretation of morbid phenomena. Hence in his “Linnaean Lecture on the Law of the Heart,”\(^3\) and in his textbook of physiology, it is the relationship between initial length of muscle fiber and the tension developed during contraction that is the center of his interest. Perhaps it is because modern investigators have been more closely acquainted with these works than with the originals that has led to some of Starling’s conclusions, which are most relevant to heart failure, being overlooked.

A paper delivered before the Washington State Heart Association, September 1958.

Starling’s Experiments

Starling’s great technical achievement was the heart-lung preparation. In this preparation, while the blood circulated through the animal’s lungs in the ordinary way, it passed from the aorta through a cannula in the brachiocephalic artery, through an adjustable resistance, then through a warming coil to the venous reservoir, and back to the heart through a cannula in the superior vena cava. The lungs not only oxygenated the blood, they removed vasoactive substances that had hitherto made difficult perfusion of organs with blood. Moreover, in this preparation right atrial inflow and aortic pressure were controlled, while pressure in the vena cava, and in the aorta, as well as cardiac output, was measured.

The experiments on which the law of the heart were based were the subject of 2 papers, the first by Patterson and Starling,\(^1\) the second by Patterson, Piper, and Starling.\(^2\) In the first paper Patterson and Starling were concerned with the mechanical factors that determined the output of the ventricles. These experiments were prompted by the controversy that had existed up to then as to the extent to which the heart could alter its output, a controversy that was due to the imperfect methods of measuring this in the whole animal. They first investigated the connection between venous inflow, ventricular output, and venous pressure. They wrote:

If we are to understand the factors responsible for the power of the heart to adapt its output to the inflow, it is necessary to study the relation of the pressures on the venous side of the heart to the volume of inflow. This relation is shown in the curves in which the venous pressures in nine different experiments, as measured on the right side of the heart, are plotted against the output (fig. 1). It will be seen that as the inflow and output gradually increase, there is a slight rise of venous pressure with each increase. The height of the venous pressure does not, however, rise in a straight line but in a curve, becoming
more rapid as the limits of the functional capacity of the heart are reached, until in some cases the heart becomes over distended, is unable to deal with the blood filling its cavities, and the output diminishes, although the venous pressure rises to a maximum. During the first part of the curve, with small to moderate output, we may say that the venous pressure, as measured at the entry of the vena cava into the right auricle, is mainly important in providing a quick flow of blood into the right auricle and ventricle, so as to maintain a slight distending force on the relaxing ventricle, so that the blood is always present to follow the ventricular wall as it relaxes. As the inflow increases still further, the pressure begins to rise more rapidly and now becomes an effective factor in distending the ventricular wall and quickening the rate at which lengthening occurs after the end of systole. It is evident that there must be some limit to the process by which rise of venous pressure causes increased filling and increased output of the heart. This limit is probably reached when the venous pressure is high enough to produce maximal distension of the heart just as the next systole begins. This explanation, however, at once brings in the further question as to the significance of maximal dilatation. Is the maximum set by the connective tissue framework of the muscular heart wall, or does it vary with the functional capacity of the heart? The fact that with a high arterial resistance the maximum possible output is smaller than with a moderate resistance would at first seem to point to the optimum distension as being dependent on the functional capacity of the heart muscle. We have found, however, that, as the arterial resistance is increased, the amount of residual blood remaining in the ventricle after each systole is also increased, so that, assuming that each heart has a constant maximum distension set by the length of its muscle fibres and the arrangement of its connective tissue, it will attain this maximum during diastole with increasing venous inflow sooner, if the arterial resistance is high, than when the arterial resistance is low. We are inclined therefore to believe that the maximum capacity of the heart is a fixed quantity for each heart and is dependent on its structural arrangements.

The effect of moderate fatigue is well shown in Exp. 2. In this animal, with a heart of 44 gms., an output of 2000 c.c. per minute was obtained at the beginning of the experiment with a venous pressure of 80 mm. Hg against an arterial pressure of 112 mm. Hg. About half an hour later in the same experiment, with the same rate of beat and the same arterial pressure, the same output of 2000 c.c. per minute was only obtained with a venous pressure of 130 mm. Hg. This experiment shows us what fatigue of the heart means. In the fatigued heart a greater diastolic distension is necessary to produce a given output of blood at each systole than is required in the fresh heart beating at the same rate. This distension can only be produced by increasing the venous pressure.

I would like to emphasize to the reader the importance of this last paragraph. If we substitute in the last 3 sentences "heart in failure" for "fatigued heart," we have clearly displayed a concept of heart failure that tallies closely with what is seen in man. Moreover, if the reader cares to compare the details of the experiment given with figure 1, he will see that the fresh and the fatigued heart are behaving so differently that their behavior would not be expressed by points on the same curve. As figure 1 shows, each curve represents an individual heart, and as experiment 2 illustrates, an individual heart in a particul-

Figure 1

Shows the relationship between venous pressure in mm. $H_2O$ (ordinate) recorded from the cannula inserted into the inferior vena cava and the cardiac output in milliliters per 10 seconds (abscissa) in nine separate experiments in the dog heart-lung preparation. In each experiment the venous inflow was increased either by raising the venous reservoir or altering the size of the clip connecting it to the cannula in the superior vena cava. After Patterson and Starling, J. Physiol. 48: 337, 1914. (Figures 1, 2, 3, 4, 6, and 7 are reproduced by courtesy of the authors and the publishers.)
lar state of fitness or tone; when its fitness alters, the position of the curve alters also.

Patterson and Starling recognized that the heart consisted of 2 pumps and they therefore measured simultaneously the pressure in the left atrium with that in the right. With regard to these experiments they say:

These results show that, in a heart that is in good condition, as the inflow is increased from a minimal to a moderate amount, the pressure in the left auricle rises at approximately the same rate as the pressure on the right side of the heart. This is what we should expect, since increased pressure in the inferior vena cava causes increased filling of the right heart and therefore increased output. The whole of this output is driven into the left auricle, so here again there must be a direct connection between venous pressure, diastolic filling and output. When, however, the demands on the functional capacity of the heart are increased by increasing the inflow into the right side of the heart to a maximum, marked differences may be found between the pressures in the right and left auricles, and these differences are especially pronounced when the heart fails or is on the point of failing. They are due to the fact that failure may commence on one side of the heart before the other, and that as a rule the side on which failure commences will be determined by the stress which is laid on it.

In their conclusions to this paper they wrote:

With a constant inflow, fatigue of the heart is shown by a rise of venous pressure accompanied by increased diastolic filling and mean volume of the heart, the outflow remaining constant.

The above statements as to venous pressure apply to both sides of the heart. When failure occurs under a maximal load, either the right or the left side of the heart may fail before the other side.

In the second paper of the series they added 2 further technical methods. They placed a cardiometer over the ventricles and were thus able to measure the volume changes with each beat of the heart, and they introduced a manometer into the cardiac cavity so that they could record the changes in pressure during the heart beat. In the course of this long and important paper they showed that when the heart was called on to increase its work because of a sudden increase in the arterial resistance, the stroke volume at first fell so that the cardiac size rose, until finally at a new and increased diastolic size, the heart was putting out its original output but at a greatly increased pressure (fig. 2). This increase in diastolic size was accompanied by an increase in the venous pressure in the right atrium. Similarly, when the inflow was increased, arterial pressure remaining constant, the heart gradually distended until, at a new and larger diastolic size, it put out a much larger outflow.
than before, this change again being effected through the increased venous pressure (fig. 3).

They wrote:

The law of the heart is therefore the same as that of skeletal muscle, namely that the mechanical energy set free on passage from the resting to the contracted state depends on the area of "chemically active surfaces," i.e., on the length of the muscle fibres. This simple formula serves to explain" the whole behaviour of the isolated mammalian heart,—its movements, powers of adaptation to varying demands made upon it, behaviour in fatigue and under the influence of its nerves or chemical agencies, such as acid ions or adrenaline.

They sum up the contrast between a heart in good condition and a heart in bad condition as follows:

It is evident from what we have said above that the word tone is properly employed as synonymous with physiological condition or fitness of the muscle fibre, and its measure is the energy set free per unit length of muscle fibre at each contraction of the heart. A good heart, i.e., one with a good tone, will carry on a large circulation against a high arterial pressure and nearly empty itself at each contraction, while a heart with a defective tone, as is the case when it is tired, can carry on the same circulation but only when its fibres at the beginning of contraction are much longer, i.e., when the heart is dilated. In the latter case the output of blood will be the same as in the former, but both the systolic and the diastolic volumes of the heart will be increased.

Fatigue of the heart may go on to heart failure. This occurs when the dilatation, which is the mechanical result of unchanging inflow and failing outflow and is the automatic means of regulating outflow to inflow, proceeds to such an extent that the tension of the muscle fibres becomes increasingly inadequate in producing rise of intracardiac pressure. The mechanical disadvantage, at which in the dilated spherical heart the skin of muscle fibres must act, finally smashes up the system and the circulation comes to an end.

Here again, in this second paper, is a clear concept of what we should now term the various stages of heart failure.

Starling was not a clinician and therefore had no opportunity to interpret his experiments and resultant views in terms of the phenomena seen at the bedside. At that time very few clinicians were in a position to do so, because they knew nothing of the venous pressure. I remember vividly being intern in 1930 to one of the best physicians whom it has been my privilege to know, whose specialty was heart disease, and who was not acquainted with the message contained in the veins of the neck. This struck me most forcibly when I was asked to transfuse a patient with mitral stenosis and severe anemia, whose jugular veins were intensely distended, as the patient sat up in bed. I knew nothing of their meaning except that I had read somewhere that this jugular venous distention was an indication for venesection. It struck me at the time as very odd that a patient who presented a sign indicating the desirability of venesection should be transfused. I was thus in a way scarcely surprised when the patient developed acute pulmonary edema as a result of transfusion and died. It was only when I came to work with Lewis that I first became acquainted with the meaning and importance of estimating the venous pressure from neck veins. Lewis had learned this partly from...
Mackenzie, but chiefly from his own use of the polygraph. As he explained to me, if one wants to get a good tracing of the jugular pulse one must apply the venous receiver at a point where distended and collapsed veins meet, that is to say at a point where the venous pressure is approximately atmospheric. He had found that this was commonly beneath the angle of Louis in normal subjects, and above it in those with cardiac failure, and he taught consistently that the venous pressure could be measured by inspecting the veins of the neck and that the height of the venous pressure was the best guide to the presence and severity of cardiac failure. Lewis wrote in Diseases of the Heart:

Study of the veins still suffers an unfortunate neglect; in these vessels are to be found some of the most valuable signs we possess in managing heart cases.

Yet curiously enough I never heard Lewis develop Starling’s thesis on the nature of cardiac failure; nor did he develop it in his book. Unfortunately, I never discussed this subject with my old chief. But though Lewis was a great friend of Starling, he was absorbed in mapping the course of the excitation process through the heart at the time Starling was making his important experiments. And I know enough of Lewis’s capacity to be absorbed in the problem of the day to suspect that this may be the explanation.

Lewis’s ideas partly arose from Mackenzie’s views on heart failure. Mackenzie wrote devastatingly against the back-pressure hypothesis and particularly against the practice of seeking the signs of cardiac failure in systolic murmurs that were held to indicate the presence of regurgitation through the atrioventricular valves. Though he never went so far as to state that the symptoms were due to reduced output of the heart, he attributed them to failure of the heart to maintain the circulation. Lewis’s views were also much affected by some experiments that he had done with Barcroft, in which he had sent blood from cardiac patients who were breathless to Barcroft, who had determined the position of the oxygen dissociation curve of hemoglobin, and thus the pH of the blood. These experiments convinced Lewis that cardiac breathlessness was due to acidity of the blood, which in turn seemed to him most probably due to diminished cardiac output. Thus, although he recognized that a raised venous pressure was the sine qua non of cardiac failure, and although he attributed this to failure of the heart to transfer blood from the venous to the arterial system, he never really interpreted Starling’s experiments in the clinical field.

One of the first clinicians to try to interpret Starling’s observations in the light of clinical experience was T. R. Harrison in his book on Failure of the Circulation, in which he showed clearly that the hypothesis of forward failure favored by the great masters Mackenzie and Lewis did not explain the phenomena of cardiac failure, which were more consistent with the alternative hypothesis of backward failure. He devoted a good deal of attention to Starling’s experiments, and particularly to his law of the heart, but he did quote the passage already described, comparing a heart in good condition with one that was tired. He went on as follows:

It is well known that an increase in venous pressure almost always accompanies advanced congestive failure, and it will be shown in Chapter 15 that patients with this disorder exhibit on exertion a rise in venous pressure which is unusually marked and unusually prolonged.

However, the modern appreciation of the importance of Starling’s experiments to the interpretation of the phenomena of heart failure in man is chiefly due to McMichael and his colleague Sharpey-Schafer. McMichael had worked in Lewis’s hospital but was not one of his pupils. Schafer was a pupil of Lewis’s. In 1938 McMichael determined the cardiac output by the acetylene method in subjects with the 4 standard grades of heart failure, both in the erect and supine positions. He showed that in group 1 (without symptoms) the cardiac output and venous pressure were normal, and that there was a considerable rise in cardiac output when the erect was changed to the supine position. This rise he attributed

*Criticism of Heart Association classification.
to the effect of venous pressure on cardiac output. In group 2b (breathless on slight exertion) cardiac output was slightly subnormal. Venous pressure was slightly raised and there was no change whatsoever in cardiac output on posture. In group 3 (breathless at rest) the cardiac output was reduced, while the venous pressure was grossly raised. Again posture was without effect.

McMichael appreciated the significance of his work in showing that in the early stages of cardiac failure the heart loses its ability to respond to a small change in venous pressure with an increase in output, and in the later stages is working at a high venous pressure. He discussed Starling's views as set out in his Linacre Lecture, his demonstrations of the interrelationship of venous pressure and cardiac output, and Wiggers and Katz's confirmation of it.10 But he did not relate his results to Patterson and Starling's curve (figure 1) with which they were in close agreement.

McMichael and Sharpey-Schafer in 194411 published their results on cardiac output determined with the aid of right atrial catheterization, in which they showed, among other things, that cardiac output in normal subjects was increased by infusion, and reduced by venesection or cuffs on the thighs, and that there was a roughly linear relationship between venous pressure and cardiac output. Later the same year they published results on the action of intravenous Digoxin in man,12 in which they showed that its most constant action in heart failure was to reduce the greatly elevated venous pressure while usually increasing cardiac output, and that a similar reduction in venous pressure and increase in cardiac output could be obtained by inflating cuffs on the thighs. They attributed the effect of Digoxin to the fall of venous pressure that it produced; they attributed the rise of cardiac output in response to the fall of venous pressure to the heart being "over the top" of Starling's curve, a drawing of which is reproduced in figure 4; and they suggested the possibility that Digoxin might have a primary action on venous pressure, the cardiac response being secondary. These wholly unexpected results naturally caused quite a stir in the world of cardiology. The following year Howarth, McMichael, and Schafer13 carried their observations further, showing that reducing venous pressure by bleeding in advanced cardiac failure also increased cardiac output. Though further observation on the action of digitalis, particularly in left ventricular failure,14 has shown that digitalis probably does act through its effect on the heart, the principal observation that in heart failure reduction of venous pressure increases cardiac output still stands. And it clearly parallels in man the phenomenon recorded by Patterson and Starling in the dog's heart.

The similarity between the heart in advanced cardiac failure and the heart at the extreme limits of its performance in Starling's experiments, to which McMichael and Schafer drew attention, naturally excited the greatest interest. The curve which they drew as Starling's curve has been widely accepted as being such. Closer inspection shows, however, that it differs from figure 1 in several particulars. Firstly, it is drawn on its side, a procedure that conforms to modern practice of making the dependent variable the ordinate. Secondly, Starling's curves were not

**Figure 4**

Starling's curve. Increase of filling pressure is accompanied by an increase in output until the heart is overloaded; thereafter the output begins to fall with any further increase in pressure. After McMichael and Sharpey-Schafer, Quart. J. Med. 37: 123, 1944.
The upper curve shows (continuous line) the line joining 2 points relating venous pressure to cardiac output in a normal subject given an intravenous infusion and venesection; the interrupted line is an imaginative continuation. The lower curve shows 2 points relating venous pressure to cardiac output in a subject with cardiac failure in whom the venous pressure was reduced by cuffs on the limbs; the interrupted line is an imaginative continuation. The imaginative curves are not thought to approximate closely to the truth since, inter alia, small errors in cardiac output will grossly alter the slopes of the lines. But they do illustrate that the behavior of the normal heart and the heart in failure clearly do not follow the same curve.

A good deal of work has been done on the dog to test the general principles of Starling’s work. For example, Sarnoff and Berglund measured atrial, pulmonary artery, and aortic pressures as well as systemic flows in otherwise intact dogs. They showed that the relationship between venous pressure and stroke work of the ventricle was different on the left and the right sides of the heart. They showed that interfering with the nutrition of the heart would alter the shapes of these curves, as would infusions of epinephrine. They go on to say:

In order to uphold the view of Frank and Starling it has been necessary to broaden this view with a spectrum or family of curves so as to have it encompass the observed phenomena. The idea of a family of Starling curves was first suggested to us by Dow in 1949. In 1952 McMichael drew three theoretical plots of cardiac work against filling pressure representing the normal, the hypodynamic and the hypertrophied heart. The theoretic curves presented by Youmans and Huekins and by Lewis and co-workers unfortunately plotted cardiac output or stroke volume against filling pressure. The data presented above and elsewhere substantially strengthen the view that a ventricle may describe many different ventricular function curves. These data also furnish examples of certain ways in which the curves may be altered.

Similarly, in Harrison’s recent text book, Dexter and Harrison state:

Starling’s curve is not a single line but rather a whole family of curves, and the curve for the right ventricle is quite different from that for the left.
Figure 7

A normal ventricle does work A at a low diastolic tension. Acute load B is accomplished at a higher filling pressure. Development of hypertrophy BC may cope with a chronic load, or the myocardium may be overstrained and become hypodynamic, BE. Hypodynamic state may also develop after physiological hypertrophy, DE. After McMichael, Brit. Med. J. 2: 525, 1952.

If the reader will read carefully the second paragraph quoted from Patterson and Starling’s paper he will see that this is what they found. A heart that is fresh and a heart that is “tired” are not on the same curve; they are on different curves. One would also surmise that the effect of digitalis is not to alter the position of the heart on a curve; it is to alter the behavior of the heart in respect to venous pressure and thus to alter the position of the curve relating venous pressure and cardiac output, a curve characteristic for that heart in that state of fitness or “tone,” to use the expression common in Starling’s time.

Intact man differs considerably from the heart-lung preparation of the dog. The filling pressure of the heart is a compound of the venous pressure and the intrathoracic pressure. Accurate measurements of cardiac output and of the filling pressure of the heart are difficult to make in severe exercise. The diastolic size of the heart is dependent not only on end-diastolic pressure, but on the time over which this pressure has operated. Nevertheless, there seems very little doubt that Starling’s curve as shown in figure 1 has only limited application to the normal human heart. The strongest evidence for this is the fact that in exercise, as shown by Liljestrand, Lysholm, and Nylin, the volume of the heart may not be much increased, even though the cardiac output is multiplied many times. Similarly the dog may be exercised to exhaustion without any appreciable rise in venous pressure. Presumably in the intact animal nervous and hormonal effects on the heart alter the contractile powers of its fibers to an extent such that the relationships worked out in the isolated heart no longer apply so simply. In resting man it is disputed whether cardiac output and venous pressure are related. In cardiac failure there is more evidence that the relationship between venous pressure and cardiac output are as depicted in the extreme ends in Patterson and Starling’s curves. Moreover there is now evidence to suggest that this part of the curve is due to regurgitation through the atrioventricular valves. Thus the anatomic condition limiting the optimal distention of the heart, which Patterson and Starling correctly surmised in 1914, seems in process of being defined.

It seems a little unfortunate that the idea should have become current that Starling ever thought of a single curve. He stated quite clearly that the difference between a good heart and a bad heart was that, for a given output, the former was working at a low diastolic size and a low venous pressure, the latter at a high diastolic size and a high venous pressure. This would seem to me to be the essence of cardiac failure as we know it in man. Whether the cardiac output is greater than it is in a normal man at rest, as for example in anemia, osteitis deformans, or emphysema, or the cardiac output is less than in a normal man at rest, as for example in rheumatic or hypertensive heart disease, the heart in heart failure is working at a high venous pressure. * In fact I would go so far

*Interestingly enough, in these circumstances, whether cardiac output be high or low, the glomerular filtration rate and the renal plasma flow are both reduced. How this is achieved is now one of the outstanding problems of the day.
as to define cardiac failure in these terms. And as can be seen from the quotations from this paper, Patterson and Starling not only realized for the first time the true nature of heart failure, they clearly saw that the right and left sides of the heart might fail separately, according to the strain that was severally imposed upon them.

In fact, then, Patterson and Starling took us pretty close to interpreting the facts of heart failure in man. When one reflects that this was the work of physiologists, not deeply conversant with heart failure (though Patterson, Starling’s son-in-law, is a highly respected physician), and that the object of study was the dog’s heart, this ranks as a great achievement, and I think one that has not been appreciated as fully as it deserves.

**Summario in Interlingua**

Es disuiteb, ab le puncto de vista del historia del concepto de disfallimento cardiac, le significacion del preparato isolate de corde e pulmon, primo utilitate in studios experimental relative al dynamica del corde del can per le physiologo E. H. Starling, le qual, in collaboration con S. W. Patterson e aleres, publicava su pertinente observationes original in iste campo in duo articulos del anno 1914. Es presentate extense citationes ab iste e altere publicationes de Starling.

Le autor conclude que Starling e Patterson non solmente esseva le primes qui recognoseeva le ver natura de disfallimento cardiac, illes etiam videva que le latere dextere e le latere sinistre del corde potte fallir separatamente in dependentia del effortio requirite ab le un o ab le altere del illos.

**References**

1. Patterson, S. W., AND Starling, E. H.: On the mechanical factors which determine the output of the ventricles. J. Physiol. 48: 357, 1914.


Starling and the Concept of Heart Failure
GEORGE PICKERING

*Circulation.* 1960;21:323-331
doi: 10.1161/01.CIR.21.3.323

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1960 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/21/3/323.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org/subscriptions/