EDITORIAL REVIEW

The Frank–Starling curve

M. I. M. NOBLE
Midhurst Medical Research Institute, Midhurst, Sussex, U.K.

A basic property of the normal heart is that if its volume is increased, there is an increase in the strength of the contraction. The phenomenon is known as Starling's Law, and as the Frank-Starling mechanism. This phenomenon is of great importance. If the heart were unable to increase its output when distended, the distension would become progressively severe.

The underlying important relation in the ventricular muscle is that between systolic contractile force and muscle (or sarcomere) length: the length-tension curve (Ciba Foundation Symposium, 1974). An example is shown in Fig. 1. A length of heart muscle is stimulated to contract but is not allowed to shorten. It therefore develops force isometrically. This is repeated for a range of different muscle lengths. Systolic contractile force (normalized for the cross-sectional area of muscle giving stress) is plotted against length as a percentage of the length at zero filling pressure. The diastolic stress curve is due to the resting elasticity of the muscle.

Molecular basis of the length–tension curve

A basic piece of information required for understanding this is the relationship between contractile force and sarcomere length in living muscle. Only recently have the necessary techniques become available and the data are still emerging (Jewell, 1977). In the rat Pollack & Kreuger (1976) obtained a linear increase in tension with sarcomere length from zero tension at 1.6 μm to maximum tension at 2.2 μm, with the maximum value maintained from 2.2 to 2.3 μm. In the rabbit Julian, Sollins & Moss (1976) obtained a linear increase in tension from about 30% of maximum tension at 2.0 μm, to maximum tension at nearly 2.3 μm; there was no plateau to the curve.

The contractile proteins consist of interdigitating arrays of thick myosin and thin actin filaments, the former 1.6 μm long in the centre of the sarcomere and the latter 1 μm long, extending towards the centre of the sarcomere from each end (Fig. 2). There are cross-projections (usually called 'cross-bridges') from the thick filaments extending laterally towards the overlapping thin filaments. These cross-projections are absent in the centre of the thick filaments so that over the range of sarcomere length 1.95–2.1 μm, the number of cross-projections in apposition to thin filaments is constant. It is clear from the results of Pollack and of Julian that there is still an increasing contractile force with increasing sarcomere length over this same range. There is no ‘descending limb’ above 2.1 μm sarcomere length where cross-bridge number decreases. There is no correlation between contractile force and cross-bridge number.

Jewell (1977) marshalls evidence to show that at shorter sarcomere lengths the muscle is not
completely activated by calcium ions. Since the activation system is dependent on depolarization of the cell membrane, the problem of incomplete activation can be overcome by removing it. In such a ‘skinned’ preparation, Fabiato & Fabiato (1975) showed that the relationship between tension and sarcomere length is very flat. The tension at 1.6 μm is still about 85% of the maximum at 2.1 μm. At sarcomere lengths below 1.6 μm, where the thick filaments are compressed, the tension still falls only to about 65% of maximum at 1.2 μm. This relationship between tension and sarcomere length represents the effect of the impediment to tension development of double overlap of thin filaments below 1.95 μm and of the compression of the thick filaments below 1.6 μm in the fully activated tissue. Thus the major part of the decrease in tension with shorter sarcomeres seems to be due to incomplete activation. This is consistent with the direct evidence obtained in skeletal muscle fibres by Taylor, Rudel & Blinks (1975) showing that calcium ion release during activation is a function of initial sarcomere length.

From these findings it emerges that the final common factor for both the Frank-Starling phenomenon and increases of contractile strength at constant sarcomere length (so-called ‘inotropic’ effects, increases in ‘contractility’) is an increase in the amount of calcium ions delivered to the contractile proteins during activation. Thus there is no fundamental difference between the two phenomena.

Relationship between the length–tension curve and the pressure–volume curve

In an intact ventricle, a plot similar to the isometric length–tension curve (Fig. 1) can be made by preventing ejection and measuring the pressure developed in systole at different volumes. Human data are not available. Dog data are presented in Fig. 3 and a volume scale appropriate for humans is added beneath. The upper continuous line represents isovolumically developed systolic pressures, and the lower continuous line diastolic pressures.

The relationship between this curve and the length–tension curve (Fig. 1) depends on the geometry of the ventricle. If we now confine ourselves to the left ventricle, it is necessary to make assumptions about the shape of the cavity, thickness of the wall etc. In the example shown, Fig. 3 was measured and Fig. 1 calculated assuming a spherical ventricle. Pressure in the ventricle is the force in the wall divided by the cross-sectional area of the cavity (Heftner, Sheffield, Cobbs & Klip, 1962). This means that as the ventricle is distended, systolic pressure (systolic force divided by an increasing area) rises less than force. Pressure is not just a function of contractile force, but is also an inverse function of volume, which is the independent variable. Thus if the length–tension curve reached a flat plateau, the isovolumic pressure would decrease with increasing volume (a descending limb). If the pressure–volume curve reached a flat plateau, tension would still be
The physiological phenomenon of increased mechanical performance in response to increased ventricular volume is the Frank-Starling mechanism. Frank (1895) studied isovolumic pressure development and found a relationship like that in Fig. 3. In order to study ejection, one needs to impose constant arterial (ventricular systolic) pressure, as in the horizontal broken line at 100 mmHg in Fig. 3. This abnormal situation, obtained by replacing the arteries with an artificial system, is necessary in order to make the following analysis. The left ventricle starting at end-diastolic volume A in Fig. 3 contracts to pressure B isovolumically, and then shortens at that pressure to end-systolic volume C. The normal ventricle always contracts to that end-diastolic volume from which it could develop pressure when contracting isovolumically, which is equal to the end-ejection ventricular pressure (Weber, Janicki & Hefner, 1976). Therefore when the end-diastolic volume is increased to D, isovolumic contraction proceeds to point E and ejection again ends at point C. The stroke volume has increased from BC (square symbol in Fig. 4) to EC (triangular symbol in Fig. 4). The increment in stroke volume BE is identical with the increment in end-diastolic volume AD so that the slope of the curve in Fig. 4 is unity.

It should be apparent from the construction of Fig. 4 that the relationship between stroke volume and end-diastolic volume gives no information about the pressure-volume or length-tension curves (Fig. 1 and Fig. 3). The idea that it does give such information is one of the most common misconceptions in cardiology. The fact is that the stroke volume/end-diastolic volume curve (Fig. 4) describes a different property of the heart (i.e. the constancy of end-systolic volume for a given end-ejection pressure) from the length–tension curve of the muscle. The same is true when any function of stroke volume (e.g. cardiac output, stroke work, minute work) is plotted against any index of end-diastolic volume (end-diastolic pressure, end-diastolic diameter).

Confusion is added by plotting stroke work instead of stroke volume (Sarnoff & Mitchell, 1962). Work is pressure times stroke volume and is a function of pressure (in Fig. 3, at the end of contraction ABC, pressure falls vertically (isovolumically) to the diastolic curve and rises during filling to point A completing the loop; the stroke

**What is the Frank–Starling curve?**

The Frank-Starling curve is a graphical representation of the relationship between ventricular volume and pressure. It is based on the principle that the pressure developed by the ventricle increases with increasing volume, up to a point where it becomes impossible to generate further pressure due to the limitations of the muscle fibers. This relationship is observed in the left ventricle of the heart, where the volume of blood in the chamber is directly proportional to the pressure it can generate during diastole, which is the relaxation phase of the cardiac cycle. The curve is often referred to as the 'Frank-Starling mechanism', named after the investigator who first described it, Ernest Starling, and his colleague, James Frank.

**Fig. 3.** Left ventricular pressure-volume curve of the dog. Upper continuous line: isovolumic systolic pressure developed from corresponding volumes. Lower continuous line: diastolic pressure arising from increasing volume. Data adapted from Weber, Janicki & Hefner (1976) with extrapolation of diastolic curve at upper end. Broken lines indicate course of ejecting beats at a systolic pressure of 100 mmHg (hypothetical in the case of contraction FC). Dotted line indicates course of an ejecting beat at a systolic pressure of 135 mmHg. Note that the volume ejected (GH) is reduced as pressure increases. LV, Left ventricle.

**Fig. 4.** Stroke volumes achieved at increasing left ventricular end-diastolic volumes. ■, Contraction ABC in Fig. 3; ●, contraction DEC in Fig. 3; ○, contraction FC in Fig. 3. Broken line indicates actual performance in an overdistended ventricle. LV, Left ventricle.
work of this beat (ABC) is given by the area within the loop. As left ventricular pressure increases, stroke work rises and then falls even though the contractile strength is constant as judged by isovolumic pressure development. Therefore left ventricular pressure must be kept artificially constant for the use of stroke work to be valid. However, in these circumstances it is only changes in stroke volume that are being measured. The use of stroke work is not recommended.

Left ventricular end-diastolic pressure is often used to substitute for volume. Since the relationship between the two is extremely curvilinear (lower continuous line in Fig. 3), great distortion of the curve results from such a substitution, as can be seen by comparing Fig. 4 and Fig. 5. This should be remembered when using this curve, particularly in the part up to a pressure of 25 mmHg.

Since the portion of the curve of interest occurs over this narrow range of low end-diastolic pressures, considerable problems arise in making measurements of the necessary accuracy (see below).

It turns out that there are a number of curves that can lay claim to the title of Frank-Starling curve. The importance of understanding their derivation and meaning cannot be overstressed.

The ‘descending limb’

From this analysis it is clear that in the physiological range there is no descending limb to the length-tension curve or the pressure-volume curve. The failure of isovolumic systolic pressure to fall with increasing diastolic pressure was demonstrated by Monroe, Gamble, LaFarge, Kumar & Manasek (1970). If the ventricle always contracts down to a point on the pressure-volume curve (Fig. 3) an increase of end-diastolic volume to F would produce a stroke volume equal to FC (Fig. 4). This is the maximum value because distension beyond F causes left ventricular end-diastolic pressure to exceed aortic pressure, so that blood flows through an open aortic valve in diastole!

In fact, an increase in diastolic pressure and volume beyond point D in Fig. 3 causes progressively increasing problems. The rising diastolic pressures causes sub-endocardial ischaemia by decreasing the diastolic pressure gradient for coronary flow (Buckberg, Fixler, Archie & Hoffman, 1972), and the extreme distension causes mitral incompetence. Thus stroke volume falls below the expected line, i.e. the broken line in Fig. 4, with a descending limb. At point F there is no pressure gradient for coronary flow, there will be no coronary flow, no oxygen supply, no contraction. The descending limb is pathological. It is nothing whatever to do with the descending limb of the length–tension curve. The factors responsible for the descending limb may be increased in disease. Ischaemia, for instance, is more likely in the presence of coronary artery obstruction, hypertension, aortic valve disease etc.

Why make measurements of the Frank–Starling relationship in patients?

The length–tension and pressure–volume curves described above pertain to a given contractile state. They can be moved up and down by changing the amount of calcium ions delivered to the contractile proteins at each given length of the fibres, i.e. by changes in inotropic state or contractility. Depression of the whole ventricle in clinical conditions may sometimes come about through such a mechanism, i.e. a true negative inotropic effect. However, in ischaemic heart disease it is extremely common for parts of the ventricle to have depressed or absent contraction, or to have paradoxical movement. Since the pressure–volume curve is depressed in the same way by both negative inotropic effects and regional disease, the use of the idea of depressed inotropic state or depressed contractility in such circumstances seems to be inappropriate. For the same reason, the use of so-called indices of contractility, many of which are invalid (Noble, 1972; Van den Bos, Elzinga. Westerhof & Noble, 1973), is not recom-
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mended, and have been found to be of little clinical value (Parmley, Diamond, Tomoda, Forrester & Swan, 1972).

The most reasonable question to ask in the first instance is: 'Is the total contraction of the ventricle depressed and by how much?'. Since contraction is defined by the pressure–volume and stroke volume/end-diastolic volume relationships (above) it is necessary to try to measure some aspects of these curves in order to answer the question.

What should be measured in a patient?

Manipulation of end-diastolic volume over a wide range with repeated volume measurements is impractical in patients. If we go back to Fig. 3 and take reasonable values of 90 ml for volume and 100 mmHg for pressure, we find a stroke volume of 45 ml. The ejection fraction (stroke volume/end-diastolic volume) is 50%. For these resting conditions at normal arterial pressure the ejection fraction gives an idea of the position of the pressure–volume and stroke volume/end-diastolic volume curves. Ejection fraction is dimensionless and therefore independent of patient size. A shift of the pressure–volume curve down and to the right causes a reduction of ejection fraction at normal arterial pressure (Fig. 6). Further depression of the ejection fraction occurs if the ventricle fails to contract down to the end-systolic volume predicted by the pressure–volume curve. Thus a single measurement of ejection fraction is the most informative, provided that ventricular systolic pressure is normal and there is no mitral incompetence or septal defect.

Ejection fraction can be estimated at cardiac catheterization by recording a left ventricular angiogram, preferably in two planes. The systolic and diastolic cavity outlines are used to calculate ventricular volumes by making assumptions about ventricular cavity shape. These assumptions are particularly gross if the usual single plane angiogram is used (Dodge, Sandler, Barley & Hawley, 1966; Green, Carlisle, Grant & Bunnell, 1967). The method is particularly liable to error in the presence of regional disease, e.g. when there is aneurysmal bulging in one area. Nevertheless, a left ventricular angiogram is extremely useful even if only used qualitatively by an experienced cardiologist. It cannot be frequently repeated for progress studies.

Intravenous injection of radioactivity enables one to image the left ventricular cavity on a gamma camera. The total radioactivity over the ventricular area can be measured throughout the cardiac cycle and averaged over a number of beats by gating the measurements in time to the ECG (Weber, dos Remedios & Jaso, 1972; Muir, Hannan, Brash, Baldwa, Miller & Ogilvie, 1977). The total radioactivity is directly proportional to the volume of blood, enabling calculation of stroke volume, end-diastolic volume and ejection fraction. The method is non-invasive and can therefore be used in out-patients and acutely ill patients. The method in my experience has two major difficulties: (1) calibration of absolute values of volume depends on the indicator dilution principle with its attendant inaccuracies; (2) ejection fraction and end-diastolic volume measurements depend on a correct subtraction for background radioactivity due to blood in the lungs, chest wall etc., a correction which depends on the shape and size of the patient's chest, the amount of adipose tissue and other imponderables. None of these drawbacks is serious when changes in cardiac performance over time are followed in a given patient. For this purpose it is the method of choice.

Attempts have been made to infer ejection fraction from echocardiography, a non-invasive method of even wider applicability than isotopic imaging in in-patients and out-patients. Unfortunately, echocardiography is particularly liable to lack of objectivity and to measurement error, particularly when a single beam of ultrasound is used to estimate ventricular dimensions. Different

![Figure 6](image_url)
parts of the heart move into the line of the beam throughout the cardiac cycle, and it is not possible to know the relation between this varying diameter and ventricular volume. The assumption is often made that the left ventricle is a cube, angled so that its sides are parallel to the ultrasound beam, i.e. measure any diameter and cube it (Gibson, 1973). Even if more reasonable assumptions are made, it is not possible to allow for regional wall dysfunction.

In the patient in the intensive care unit, angio-

graphy is impractical and a gamma camera is usually not available. One must therefore use values for stroke volume or cardiac output and pulmonary venous pressure obtained with balloon catheters in the pulmonary artery (Swan, Ganz, Forrest, Marcus, Diamond & Chonette, 1970). These values explore only the stroke volume/end-diastolic pressure relationship (Fig. 5) and give no information about the pressure–volume curve. It is also possible, if clinical circumstances permit, to make repeat measurements after small fluid infusions and to construct a rough ‘Frank–Starling curve’. Over the course of time an impression can be gained about whether the position of the curve is changing. There are problems in making accurate measurements. There is considerable measurement variability in indicator-dilution methods for cardiac measurements. There is considerable measurement variability in indicator-dilution methods for cardiac output and stroke volume determination. In the absence of an intrathoracic pressure reference, there are respiratory swings of left ventricular end-diastolic and pulmonary venous pressure and values become a function of the arbitrary zero reference used instead. These sources of variability must be reduced by applying rigid standardization. Taken with the necessary care, these measurements are the most useful and informative in the setting of intensive care (Parmley et al., 1972).

Conclusions

1. Newer information from animal work indicates that the dependence of cardiac performance on the initial length of the myocardial fibres is related to the degree of activation of the contractile system by calcium ions.

2. There is no generally accepted definition and meaning for the term ‘Frank–Starling curve’. The pressure–volume and stroke volume/end-diastolic volume relationships are different, and describe different properties of the heart. There are a number of variants of the stroke volume/end-diastolic volume relationship referred to as Frank–Starling curves. It is therefore necessary to define precisely the variables being correlated.

3. The application of the physiological knowledge to clinical medicine remains limited. The most useful measurement is the ejection fraction, because of the way it is affected by the position of the pressure–volume curve. Improved methods of making this measurement accurately and repeatedly in various clinical states are required.

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