

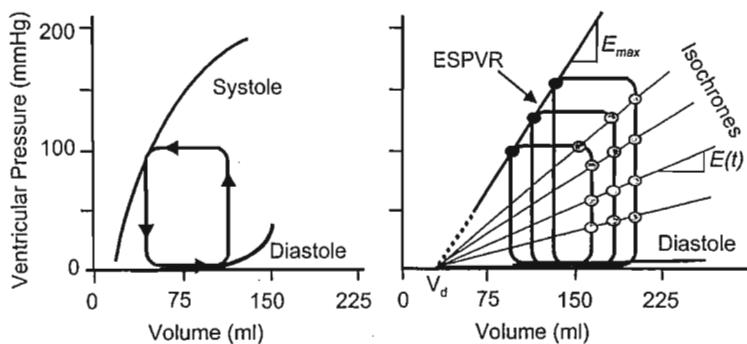
## Description

Otto Frank studied pressure-volume relations in the isolated frog heart. He found different End-Systolic Pressure-Volume Relations,  $ESPVR$ 's, for the ejecting heart and the isovolumically contracting heart. In other words, a single unique End-Systolic Pressure-Volume Relation did not appear to exist.

The same measurements in the isolated blood perfused dog heart, where volume was accurately measured with a water-filled balloon, showed that the End-Systolic Pressure-Volume Relation was the same for ejecting beats and isovolumic beats. The original results suggested a linear  $ESPVR$  with an intercept with the volume axis,  $V_d$ . The linear relation implies that the slope of the  $ESPVR$ , the  $E_{max}$ , with the dimension of pressure over volume (mmHg/ml), can be determined. Increased contractility, as obtained with epinephrine, increased the slope of the  $ESPVR$  but left the intercept volume,  $V_d$ , unchanged [5]. Therefore, the  $E_{max}$  could quantify contractility. Later it

turned out that both the diastolic pressure-volume relation and the ESPVR are not linear. The slope depends on the pressure and volume chosen and when approximating this locally with a straight line a virtual intercept volume is obtained, which may be positive or negative. However, the load-independence of the ESPVR is generally shown to be true and this is of great significance in the understanding and characterization of cardiac pump function. The load-dependence of the  $E(t)$  curve is small but does exist [2,5]. An extensive treatment is given in [2].

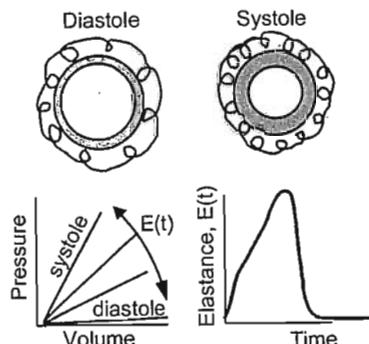
### The varying elastance model



**THE PRESSURE-VOLUME RELATION** is almost always presented as linear. This approximation may not always be correct and it may lead to, for instance, negative volume intercepts.

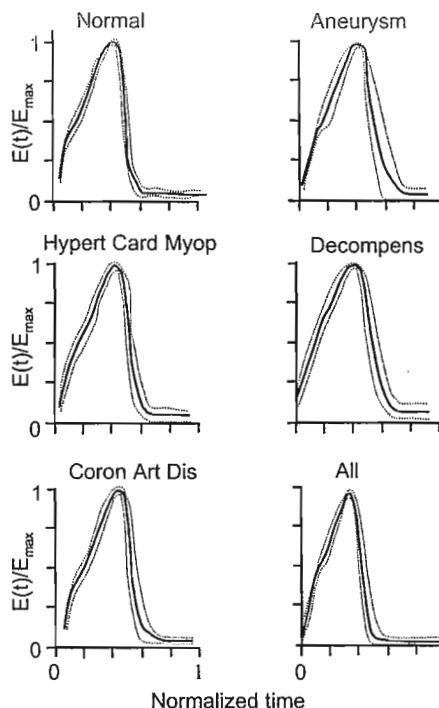
Pressure-volume loops can be analyzed by marking time points on the loop. When different loops are obtained and the times indicated, we can connect points with the same times, and construct isochrones. The slopes of the isochrones can be determined, and the slope of an isochrone is the elastance at that moment in time. The fact that the elastance varies with time, leads to the concept of time-varying elastance,  $E(t)$ . This means that during each cardiac cycle the elastance increases from its diastolic value to its systolic value  $E_{max}$  and then returns to its diastolic value again.

It has been shown that the  $E(t)$  curve, when normalized with respect to its peak value and to the time of its peak (see figure on the next page), is similar for normal and diseased human hearts [4]. Similar  $E(t)$  curves are found in the mouse, the dog and the human. It thus seems that there exists a universal  $E(t)$  curve in mammals including man, which is unaltered in shape in health and disease. The only differences between hearts and state of health are in the magnitude and time of peak of the  $E(t)$ . This similarity of the varying  $E(t)$ -curve is very useful to construct lumped models of the heart [3].



**THE VARYING ELASTANCE** concept assumes that the muscle stiffness increases from diastole to systole and back. This change in stiffness, expressed in the elastance curve is assumed to be unaffected by changes in load.

However, some doubt has been cast on the invariance of the normalized  $E(t)$  curve [1].



**THE DISEASE-INDEPENDENT  $E(t)$  curve.** The  $E(t)$  curve, when normalized in amplitude and to time to peak, is similar in many disease states. Adapted from [4], used by permission.

(US-Echo, X-ray, MRI). Pressure can be measured invasively only. Aortic pressure during the cardiac ejection phase can be used as an acceptable approximation of left ventricular pressure to determine the systolic part of the pressure-volume loop. Methods allowing for the calculation of ascending aortic pressure from peripheral pressure (Chapter 26) could, if proven sufficiently accurate, allow for a completely non-invasive determination of  $E_{\max}$ .

### Physiological and clinical relevance

The ESPVR and  $E_{\max}$  together with the diastolic pressure-volume relation, are important measures of cardiac pump function and they are often used in animal research. Clinical use is still limited but increasing. The  $E(t)$  curve depends on heart size and thus on body size. Pressures are similar in different animals but volumes are not. Volumes are proportional to body mass (Chapter 30). Thus  $E_{\max}$  can be normalized with respect ventricular lumen volume (see Chapter 11) or to heart mass or body mass to compare mammals. In diseased states the ratio of  $E_{\max}/E_{\min}$  may be a better measure of contractility than  $E_{\max}$  alone (Chapter 30).

### Determination of $E_{\max}$

The maximal slope of the pressure-volume relation is called maximal elastance,  $E_{\max}$ . It is also called End-Systolic elastance,  $E_{es}$ . To determine  $E_{\max}$  one needs to measure several pressure-volume loops to obtain a range of end-systolic pressure-volume points (see figure in the introductory box). The determination should be done sufficiently rapidly to avoid changes in contractility due to hormonal or nervous control systems. Both changes in arterial load and diastolic filling may in principle be used, but the former may illicit contractility changes. Changes in filling are therefore preferred and are also easier to accomplish in practice. For instance, blowing up a balloon in the vena cava may decrease filling over a sufficiently wide range and can be carried out sufficiently rapidly to obtain an accurate ESPVR.

Both ventricular pressure and volume should be measured on a beat-to-beat basis. Volume can be measured in a number of ways, including non-invasive techniques

be measured invasively only. Aortic

pressure during the cardiac ejection phase can be used as an acceptable

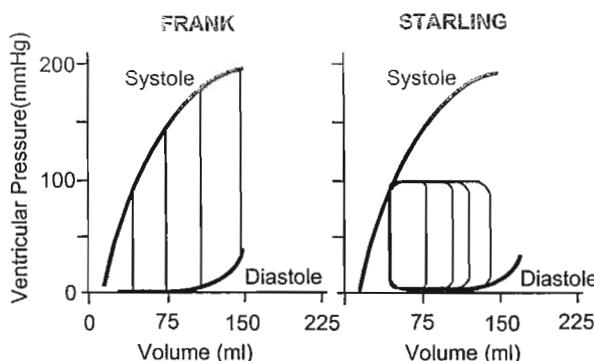
approximation of left ventricular pressure to determine the systolic part of the

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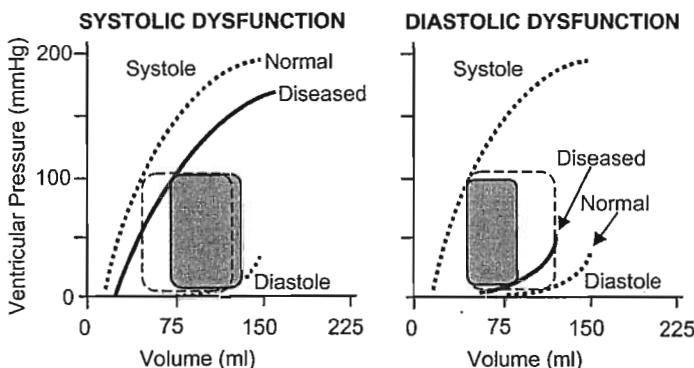
*The Frank-Starling law*

*FRANK* (left, isovolumic contractions) and *STARLING* (right, ejections against constant systolic pressure) experiments to show the effect of ventricular filling in terms of pressure-volume relations.

experiments the aortic pressure was kept constant. This in turn implies that ventricular pressure during ejection was also constant. The increase in filling resulted in an increase in Stroke Volume and thus in Cardiac Output.

*Systolic and diastolic dysfunction.*

It is important to realize that both diastole and systole play an important role



**SYSTOLIC AND DIASTOLIC DYSFUNCTION** are shown here by fully drawn lines. In systolic dysfunction the ESPVR is decreased and Stroke Volume is as well. In diastolic dysfunction filling is decreased and, although filling pressure may be higher, Stroke volume is decreased.

in cardiac function. This can be illustrated with the following example. Systolic dysfunction results in a decreased Stroke Volume, when not compensated by heart rate or diastolic filling. Diastolic dysfunction, with a stiffer ventricle in diastole causes decreased filling and higher filling

The varying elastance concept contains both Frank's and Starling's original experimental results, as shown in this figure. Frank studied the frog heart in isovolumic and ejecting beats, but we show here how isovolumic contractions behave in the pressure-volume plane when diastolic volume is increased. Starling also changed diastolic filling but studied an ejecting heart, which was loaded with a Starling resistor. This meant that in his

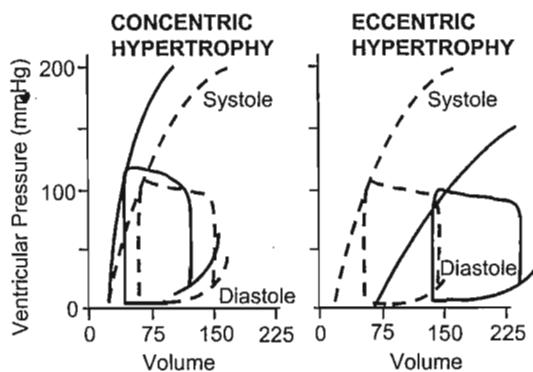
pressure. This results in a decreased Cardiac Output, and an increased pulmonary venous pressure, the latter leading to shortness of breath.

### *Concentric and eccentric hypertrophy*

Concentric and eccentric hypertrophy are interesting examples in the context of the varying elastance concept and the pressure-volume relation.

Concentric hypertrophy implies an increased wall thickness with similar lumen volume. This means a stiffer ventricle in diastole and in systole, i.e., both  $E_{max}$  and  $E_{min}$  are increased. The increase in  $E_{max}$  does not necessarily imply increased contractility of the contractile apparatus of the muscle but is mainly a result of more sarcomeres in parallel, a thicker fiber and increased wall thickness. Concentric hypertrophy leads to increased diastolic filling pressure and higher systolic pressure but similar Stroke Volume.

In eccentric hypertrophy the ventricular lumen volume is greatly increased, more sarcomeres in series, and longer cells, while the wall thickness may be unchanged or somewhat increased. The shift of the pressure-volume relation to larger volumes in eccentric hypertrophy implies, by virtue of the law of LaPlace, that wall forces are increased. The increased  $V_d$  in eccentric hypertrophy emphasizes that the slope of the ESPVR cannot be determined from a single pressure and volume measurement because this is allowed only under the assumption that the intercept volume is negligible or known. Thus at least two points on the relation are



SCHEMATIC DRAWINGS OF PRESSURE-VOLUME relations in control (dashed lines) and severe concentric hypertrophy (left) and severe dilatation (right), fully drawn lines.

required, necessitating a change in filling or systolic pressure. The shift of the pressure-volume relation to larger volumes in eccentric hypertrophy implies that wall forces are increased (LaPlace, Chapter 9).

### *Modeling on the basis of the varying elastance concept*

The finding that the normalized  $E(t)$  curve appears to be quite independent of the cardiac condition, and that it is similar in mammals (Chapter 30) allows quantitative modeling of the circulation [3,6].

### *Limitations*

It should be emphasized that the time varying elastance concept pertains to the ventricle as a whole. It allows no distinction between underlying cardiac pathologies. For instance, asynchronous contraction, local ischemia or infarction etc., all decrease the slope of the End-Systolic Pressure-Volume Relation.

The pressure-volume relations are not straight. The diastolic relation is, as in most biological tissues, convex to the volume axis. The systolic pressure-

volume relations may be reasonably straight when muscle contractility is low.

They become more and more convex to the pressure axis with increasing contractility. A curved relation implies that the  $E_{max}$  depends on volume and pressure. It is customary to approximate the ESPVR's in the working range by a straight line. Although this sometimes gives an acceptable approximation of reality, often a negative, and thus a virtual,  $V_d$  is found by linear extrapolation of the ESPVR to the volume axis.

In the normal heart the intercept volume may be small, and when this is the case the  $E_{max}$  can be estimated from a single pressure-volume loop. However, when  $V_d$  is not small, large errors will result by using a single point estimation of the End-Systolic Pressure-Volume Relation to derive  $E_{max}$ , (see figure on eccentric hypertrophy).

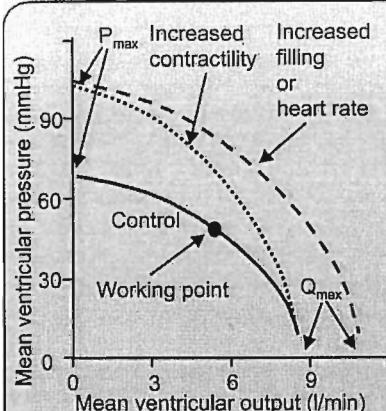
**THE END SYSTOLIC PRESSURE-VOLUME relation extends to a negative volume intercept, and a virtual  $V_d$ , which is different from the actual  $V_d$ . When only a single pressure-volume loop is studied assuming that  $V_d = 0$  the wrong  $E_{max}$  is found.**

### eccentric hypertrophy).

It has been shown by a number of investigators that load changes affect the End-Systolic Pressure-Volume Relation. However, the effect is rather small and may be due to the fact that, at high loads, the duration of ejection is curtailed and may not be long enough for  $E_{max}$  to be attained [2].

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**THE HEART AS A PUMP** can be described by the pump function graph, the relation between mean left ventricular pressure and cardiac output. A pump function graph completely describes the heart as a pump [1]. This concept is based on the characterization of industrial pumps. Here a schematic drawing of the pump function graph of the heart is shown. When the load on the heart is increased, it will generate a higher pressure but a lower cardiac output, and vice versa, and a curved inverse relation is found between mean left ventricular pressure and cardiac output. Contractility, diastolic filling and heart rate modify the relation. Increased contractility 'rotates' the pump function graph around the intercept with the flow axis,  $Q_{max}$ , as shown by the dotted line. When diastolic filling is increased or when heart rate is increased the pump function graph shifts in a 'parallel' manner, as shown by the dashed line. Thus

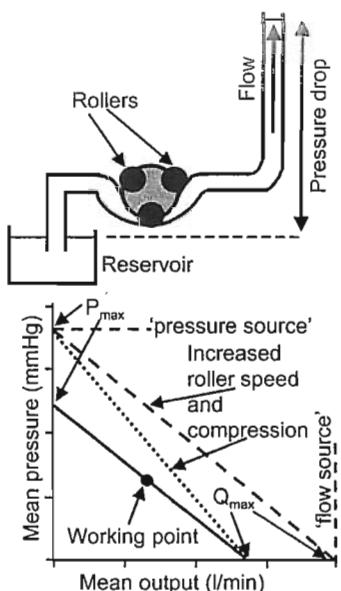
when a pump function graph is to be determined contractility, diastolic filling and heart rate should be kept constant. The working point, i.e., the pressure and flow during normal function at rest is indicated. The maximal mean pressure, i.e., the intercept with the flow axis, is the pressure when the heart beats isovolumically. The cardiac pump function graph is indirectly related to the force-velocity relation of muscle (see Chapter 12). There is also a simple relation between the pump function graph and the pressure-volume relationship.

## Description

The heart is a pump that generates pressure and flow. It can be compared with other hydraulic pumps that are usually characterized by their head (pressure) - capacity (flow) curve. As an example consider a roller pump and make a pressure-flow relation by changing the load on the pump.

In the figure on the next page we show the pump function graph of a roller pump used in the laboratory and in heart-lung machines. The pump function graph depends on the roller speed and on how much the rollers compress the tube. A higher speed gives larger pressures and flows, pressure and flow intercept,  $P_{max}$  and  $Q_{max}$ , increase. Better compression of the rollers, increases the pressure generating capability because less leakage is present, the  $P_{max}$  increases. Since at low pressures the leakage is negligible, the maximal flow,  $Q_{max}$ , is hardly affected by changes in compression of the tube. Thus the result of the increased roller compression is a clockwise 'rotation' of the pump function graph around the intercept with the flow axis.

We use the term pump function graph for the pressure-flow relation. The pump function graph of a roller pump can be determined by changing the resistance in the outflow tube, while keeping the pump characteristics the same. Thus roller speed and the inflow pressure level are kept constant. For very high resistance values the pressure is maximal,  $P_{max}$ , but the flow is negligible. When the resistance is negligible flow is maximal,  $Q_{max}$ , but the generated pressure is zero. Thus, an inverse relation between pressure and flow generated is obtained. The relation happens to be straight for this type of pump, and gives information about what pressures and flows the pump can generate. The pump function graph also shows that this particular pump is



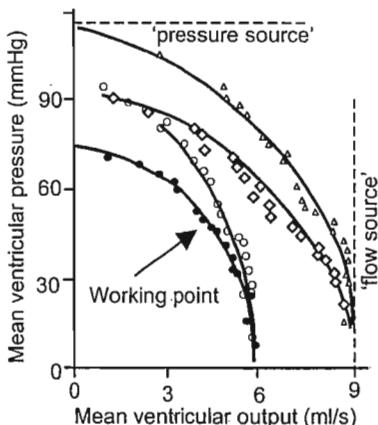
**THE PUMP FUNCTION GRAPH** of a roller pump. A laboratory pump is shown on the left. When roller speed and compression of the tube by the rollers is kept constant a pump function graph can be determined by changing the load of the pump, here obtained by changes in height of the outflow tube. When roller speed is increased or tube compression is increased the dashed and stippled relations are found, respectively. Adapted from [1], used by permission.

analogy with the derivation of arterial input impedance.

From the pump function graph we can see that the heart decreases its output when a higher pressure is generated. In other words the heart does neither generate the same flow, nor the same pressure under different loading conditions. This means that the heart is neither a pressure source, i.e., the same pressure is generated independently of the load, nor a flow source i.e., the same flow for all loads. At low flows the heart behaves approximately as a

neither a pressure source, i.e., always generating the same pressure, nor a flow source, i.e., always keeping flow constant.

We can perform a similar experiment on the heart. To avoid changes in pump function by humoral and nervous control mechanisms, these studies were originally carried out in the isolated perfused and ejecting heart. When ventricular filling pressure, cardiac contractility and heart rate are kept constant, variation in the load on the heart by either changing peripheral resistance or arterial compliance, or both, results in changes of mean left ventricular pressure and mean flow [1]. Ventricular pressure and flow are related because both quantities pertain to the cardiac side of the very nonlinear aortic valves. Mean ventricular pressure and mean flow used as a first order approximation, comparable with the mean aortic pressure and mean flow to determine peripheral resistance. In principle Fourier analysis (Appendix 1) of ventricular pressure and flow can be used to derive the oscillatory aspects of the pump function graph, in



**PUMP FUNCTION GRAPHS** as originally measured in an isolated pumping cat heart preparation. The filled circles give the control situation. An increase in contractility 'rotates' the graph around the intercept with the flow axis (open circles). The two other graphs are found during increased diastolic filling (open diamonds) with a subsequent increase in contractility (triangles). Adapted from [4], used by permission.

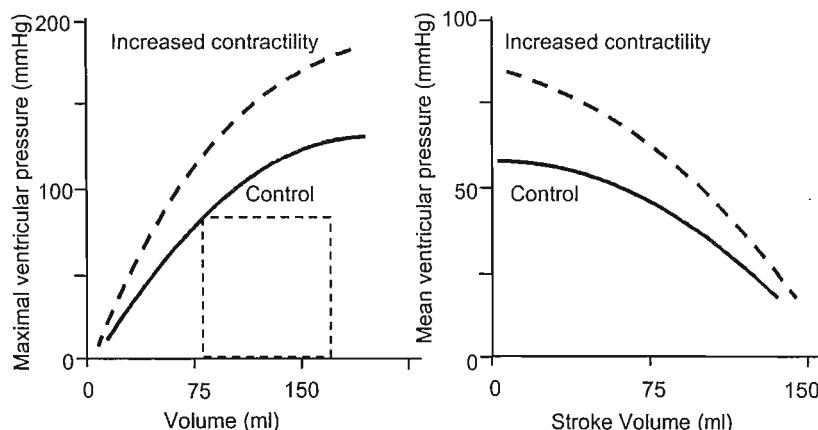
pressure source and at high flows a flow source is approached. The intercept of the pump function graph with the pressure axis is the mean isovolumic ventricular pressure, it is the mean ventricular pressure for a non-ejecting or isovolumic beat. The intercept with the flow axis is the Cardiac Output for the 'unloaded' or 'isobarically contracting' heart, i.e., contractions without build up of pressure.

The changes in contractility and filling are shown in the figure. Increased heart rate in the physiological range results in a parallel shift of the pump function graph, which is approximately proportional to the heart rate increase. An increase in cardiac contractility rotates the pump function graph around the flow intercept,  $Q_{max}$ .

At the intercept of the pump function graph with the pressure and flow axes,  $P_{max}$  and  $Q_{max}$ , respectively, the product of pressure and flow is zero and the external power is therefore negligible as well [3]. Thus external power generation exhibits a maximum for intermediate values (Chapter 15).

The pump function graph relates directly to basic properties of the cardiac muscle [2].

#### *Relation between the pump function graph and the pressure-volume relation*

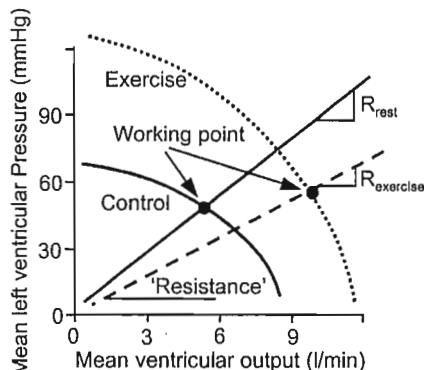


**THE PUMP FUNCTION GRAPH (right) AND THE END-SYSTOLIC PRESSURE-VOLUME RELATION (left)** show a 'mirrored' relationship. Increased contractility rotates the lines. The pump function graph is here plotted in terms of stroke volume instead of mean flow. Note the scale difference in the pressure axes.

This figure shows the qualitative relation between the pressure-volume relation and the pump function graph [7]. The pump function graph is here given in terms of Stroke Volume to make it more comparable with the pressure-volume relation, where heart rate is not represented. We see a 'mirrored' relation between the two characterizations of the heart. This follows from the fact that Stroke Volume is the decrease in ventricular volume during ejection. The main difference between the relations is that in the pressure-volume relation the end-systolic pressures, is used while in the pump function graph the mean ventricular pressure is used.

### Physiological and clinical relevance

The pump function graph describes the pump function of the heart for constant filling, heart rate and contractility. The pump function graph teaches us that the heart is neither a flow source nor a pressure source. The flow source or in German the 'Harte Brunne' was the assumed heart model used up until the 1960's. We see that contractility at constant loading pressure has only a small effect on Cardiac Output. Heart rate and diastolic filling contribute importantly to CO.



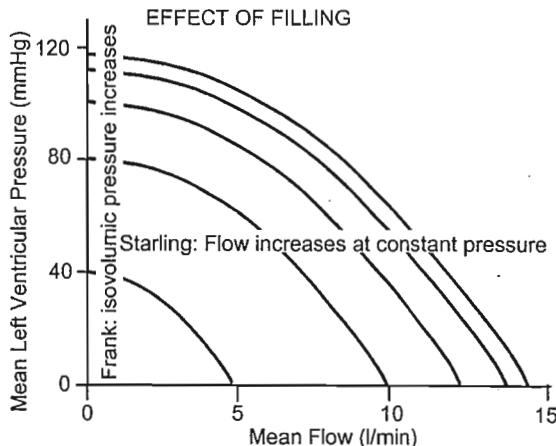
**DURING EXERCISE** vascular resistance decreases and the slope of the pump function graph increases. The cardiac output increases strongly with a limited increase in pressure.

### Exercise

The graph on the left shows what happens in moderate exercise. Due to the increase in heart rate, and the (small) increase in filling and the increase in contractility, the pump function graphs shifts outward, with a small rotation as well. The increase in heart rate forms the major contribution to the outward shift of the pump function graph. The systemic vascular resistance is decreased. The overall result is an increase in Cardiac Output with only a small increase in pressure.

### The Frank-Starling Law

This figure shows the effect of filling on the pump function graph and its meaning with respect to the Frank-Starling mechanism. Frank studied the effect of filling on isovolumic contractions. The effect of an increase in ventricular filling on non-ejecting, i.e., isovolumic, contractions is given by the intercepts of the pump function graphs with the pressure axis. Starling studied in the heart-lung preparation the effect of filling on Cardiac Output when aortic pressure was kept constant. The horizontal line represents this: Cardiac Output increases with cardiac filing.



**THE CARDIAC PUMP FUNCTION GRAPH** is a generalized description of the Frank-Starling mechanism. With increased filling the graph moves outward. One of Frank's experiments pertains to isovolumic conditions where pressure increases with filling. Starling's experiment is one that keeps aortic pressure constant so that cardiac output increases with filling.

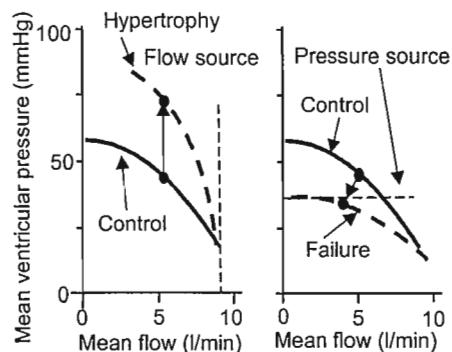
Cardiac Output increases with cardiac filing.

*Concentric hypertrophy and heart failure*

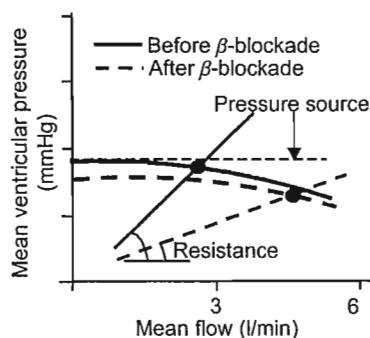
The figure shows the pump function graph in hypertension and failure. In hypertrophy a flow source is approached while in failure the heart acts more like a pressure source [5].

These changes in pump function have an effect on reflected waves returning from the periphery. A flow source means two things: the flow is not affected by reflected waves but pressure is completely reflected and thus augmented, 'closed end reflection'. Inversely, a pressure source implies that pressure is not affected by the reflected wave but the flow fully reflected and thus is decreased by the reflection.

Therefore in hypertrophy the backward pressure wave, is reflected at the heart (flow source) and is added to the forward pressure resulting in augmentation of the wave. The reflection and extra augmentation of pressure in hypertrophy shows the contribution of the hypertrophied heart to hypertension. In failure, when the heart approaches a pressure source the reflected flow wave affects the forward flow wave negatively resulting in a decrease in Cardiac Output (Chapters 21 and 22). Understanding of the contribution of the heart to reflected pressure and flow waves may assist in giving suggestions for possible therapy [8].



*THE PUMP FUNCTION GRAPH in hypertrophy and failure. The graph in hypertrophy has a larger slope in the working point, indicating that the heart approaches a flow source. In failure a pressure source is approached. The dots give the working points. Reflections against a flow source augment the pressure without affecting the flow. Reflection against a pressure source, as in failure, decreases flow but does not affect the pressure. Thus in failure cardiac output is diminished by reflections.*



*THE PUMP FUNCTION GRAPH shows that in failure a pressure source is approached. A decrease in contractility in combination with vasodilation affects pressure little but increases cardiac output*

From the figure on the left it also becomes clear why, in chronic failure beta-blockers may be beneficial even though blood pressure may be low. A decrease in contractility combined with vasodilation does, because of the 'pressure source' behavior of the heart, affect pressure little but increases cardiac output. Improved survival by beta-blockade was indeed shown in patients with severe chronic heart failure [6].

*Limitations*

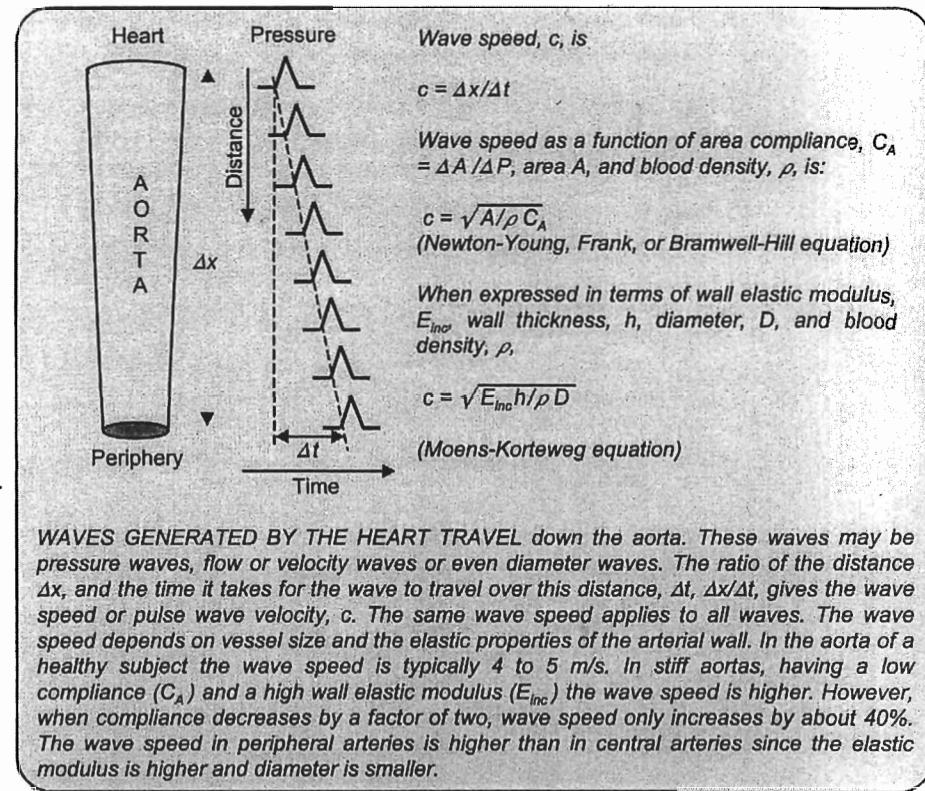
The pump function graph is a global description of the heart as a pump. Changes in muscle contractility, in synchronicity or effects of local ischemia or infarction, all affect this global description.

Since the heart is under the influence of

nervous and humoral control, and the fact that diastolic filling shifts the pump function graph, the determination of the pump function graph *in situ* is difficult. During arterial load changes filling, heart rate and contractility may change due to control mechanisms so that the operating points move over a family of pump function graphs.

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### Description

The heart generates pressure and flow waves. Because of the elasticity of the aorta and the major conduit arteries, the pressure and flow waves are not transmitted instantaneously to the periphery, but they propagate through the arterial tree with a certain speed, which we call wave speed or pulse wave velocity ( $c$ ). In analogy to waves created by the drop of a stone on the surface of a lake, wave travel is characterized by the finite time it takes for the disturbance (wave) to cover a certain distance. The distance traveled by the wave over the time delay gives the wave speed, as schematically shown in the figure in the box. Also, in analogy with the stone dropped in the lake, the wave transmission takes place even in the absence of blood flow and is not related to the velocity of the blood. When a stone is dropped in a river, the waves superimpose on the water flow, and the wave fronts traveling downstream go faster than the wave fronts that move upstream. In other words, the velocity of the blood adds to the wave speed. However, since blood flow velocity is much smaller than wave velocity this effect is usually neglected.

### Wave speed depends on vessel compliance

The wave speed can be related to the elasticity of the wall material via the Moens-Korteweg equation:

$$c = \sqrt{\frac{h \cdot E_{inc}}{2 \cdot r \cdot \rho}} = \sqrt{\frac{h \cdot E_{inc}}{D \cdot \rho}}$$

where  $E_{inc}$  is the incremental elastic modulus,  $\rho$  the blood density,  $h$  the wall thickness and  $r, D$  the lumen radius and diameter. This equation is derived for non-viscous fluid but it is a good approximation for conduit arteries filled with blood. From the Moens-Korteweg equation, Frank (1920, [3]) and Bramwell and Hill (1929, [2]) derived another expression relating wave speed to compliance:

$$c = \sqrt{\frac{A}{\rho \cdot C_A}} = \sqrt{\frac{V \cdot \Delta P}{\rho \cdot \Delta V}}$$

with  $A$  the lumen area,  $C_A = \Delta A / \Delta P$  the area compliance, and  $\rho$  is blood density. Newton and Young derived this equation first and therefore it is also often called the Newton-Young equation.

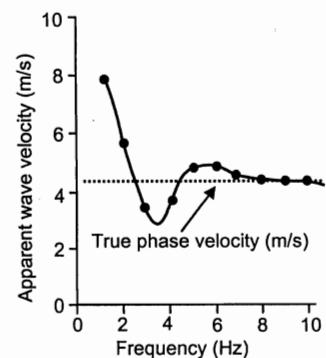
### Phase velocity and apparent phase velocity

The phase velocity is essentially the wave speed determined by the properties of the vessel wall and blood density as presented above, i.e., the effects of reflections (Chapter 21) are not included. When two arterial pressures are measured these waves include the effect of reflections and with reflection present the formulas become more complex. When Fourier analysis is performed on two waves measured a distance  $\Delta x$  apart, the wave speed for each harmonic can be obtained by using the phase lag  $\Delta\phi$  between the two harmonics. The apparent wave velocity,  $c_{app}$ , is then calculated for each harmonic as

$$c_{app,i} = \frac{2\pi \cdot \Delta x}{T_i \cdot \Delta\phi_i} = \frac{2\pi \cdot f_i \cdot \Delta x}{\Delta\phi_i}$$

with  $T_i$  the period, and  $f_i$  the frequency of the  $i^{\text{th}}$  harmonic. If the frequency is given in Hz,  $\Delta x$  in cm, and  $\Delta\phi$  in radians,  $c_{app}$  will be in cm/s. The apparent wave velocity includes the effect of reflections and is therefore not a good measure of vessel compliance. The figure on the left shows the apparent wave velocity as a function of frequency. For high frequencies the apparent wave velocity approaches the true phase velocity because for high frequencies reflections become negligible (Chapter 23).

When the wave speed is determined from



THE APPARENT WAVE VELOCITY is close to the phase velocity for high frequencies.

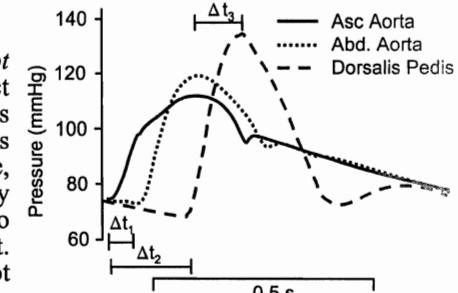
the foot of the wave the value is close to the apparent wave velocity at high frequencies and thus close to the phase velocity, so that we can obtain, from the foot-to-foot pulse wave velocity, information on vessel compliance.

### Methods to obtain wave speed

- **Time delay or foot-to-foot method.** This is the most direct method. Wave speed is estimated from the time it takes for the foot of the pressure, diameter, or blood velocity wave, to travel between two sites a known distance apart. The so calculated foot-to-foot wave velocity is close to the phase velocity and can be used to derive vessel compliance. The figure on the left shows

realistic time delays for pressure waves recorded in the human aorta and the lower limbs [6]. For instance, the delay of the foot of the wave between ascending and thoracic aorta is  $\Delta t_1 = 0.056$  s, and the distance is  $\Delta x_1 = 0.25$  m. Thus, the resulting aortic wave speed,  $c$ , equals  $0.25/0.056$  m/s or  $c = 4.5$  m/s. The average wave speed from the aorta to the lower limb is  $\Delta x_2/\Delta t_2 = 1.25$  m/0.175 s or  $c = 7.1$  m/s. Peripheral arteries are smaller, have relatively larger wall thickness, and are stiffer (higher  $E_{inc}$ ). Therefore, by virtue of the Moens-Korteweg equation, they have a higher wave speed. Note that the estimated aorta-to-dorsalis pedis wave speed is an average wave speed for the entire arterial pathway traveled by the wave (aorta, iliac, femoral, popliteal). The foot-to-foot method has been used in the above example to obtain the average wave speed between the ascending aorta and dorsalis pedis, with the foot-to-foot time delay being estimated as  $\Delta t_2 = 0.175$  s. If one had used the time delay based on peak systolic pressure ( $\Delta t_3 = 0.102$  s, in the figure), the estimated wave speed would have been  $c = 1.25$  m/0.102 s = 12.3 m/s. This speed is much higher than the foot-to-foot method estimate of  $c = 7.1$  m/s. The overestimation is attributed partly to the fact that the artery is stiffer at higher distending pressures but is also partly attributed to wave reflections at peak systole. It is therefore generally accepted that the time delay should be calculated from the foot or the up-slope of the wave rather than the systolic part.

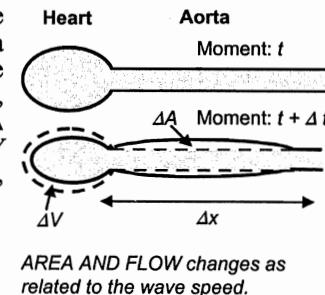
- **Wave speed derived from pressure and diameter measurements.** The Newton-Young equation permits the direct calculation of wave speed based on lumen cross-sectional area ( $A = \pi D^2/4$ ) and area compliance  $C_A$ . Simultaneous measurements of lumen diameter and pressure can be obtained using ultrasound and photoplethysmography or tonometry, respectively. Calculation of area gives the cross-sectional area-pressure relation. Based on compliance and area and using Newton-Young equation, wave speed can be derived as a function of pressure.



PRESSURE WAVES at different locations of the human arterial tree. Adapted from [6], used by permission.

*Wave speed derived from flow and area measurements.* This method, see figure, is not often used, mainly because noninvasive flow and area measurements were not available in the past. MRI and ultrasonic technologies make it possible today to perform these noninvasive measurements. Imagine that the heart ejects into the aorta a certain volume  $\Delta V$  over a period  $\Delta t$ . The ejected volume will be 'accommodated' in the aorta by means of an increase in the aortic cross-sectional area  $\Delta A$  over a certain length  $\Delta x$ . The wave speed is the speed with which the perturbation in area,  $\Delta A$ , has traveled in the aorta, which is  $\Delta x/\Delta t$ . The volume ejected in the aorta is  $\Delta V = \Delta A \cdot \Delta x$  or  $\Delta x = \Delta V/\Delta A$ . Dividing by  $\Delta t$ , we obtain:

$$c = \frac{\Delta x}{\Delta t} = \frac{\Delta V}{\Delta t \cdot \Delta A}$$



or since  $\Delta V/\Delta t$  is equal to the volume flow  $\Delta Q$

$$c = \frac{\Delta Q}{\Delta A}$$

From this relation we see that when ejection takes place in a stiff artery where the change in area,  $\Delta A$ , will be small, the wave speed will be high.

### Physiological and clinical relevance

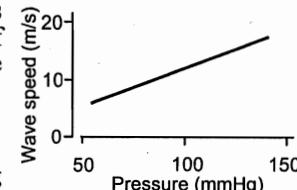
The above equations show that from wave speed wall elasticity ( $E_{inc}$ ) and area compliance  $C_A$  can be derived if the artery's geometry (diameter and wall thickness) is known, thus, giving a good estimation of large vessel elasticity.

### Time delay or foot-to-foot method

The wave speed between carotid artery and iliac or femoral artery can be measured noninvasively and is accepted as representative for aortic wave velocity. The wave speed allows estimation of aortic elasticity, and this noninvasive method is often used in hypertension research. The estimation of aortic length should account for the carotid length where the signal is measured. With aging the aorta becomes tortuous which results in an underestimation of length and thus also an underestimation in wave speed.

### Wave speed depends on pressure

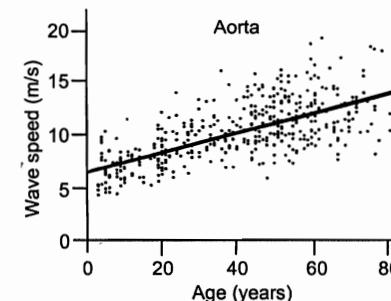
Based on compliance and area and using Newton-Young equation, wave speed can be derived as a function of pressure as shown here. Clearly wave speed is a strong function of pressure, due to the nonlinear elastic properties of the arterial wall.



WAVE SPEED as a function of pressure derived from diameter and pressure measured non-invasively in the human brachial artery.

### Wave speed depends on age

With age, wave speed increases as shown in this figure where data were measured in normal human subjects, in the absence of atherosclerosis. The increase in wave speed by about a factor two between the ages 15 and 80 years implies a decrease in compliance by a factor four. The increase in aortic stiffness with age is primarily attributed to a progressive thinning, fraying and fracture of elastic laminae, likely due to repetitive cyclic stress of the pulsing pressure.

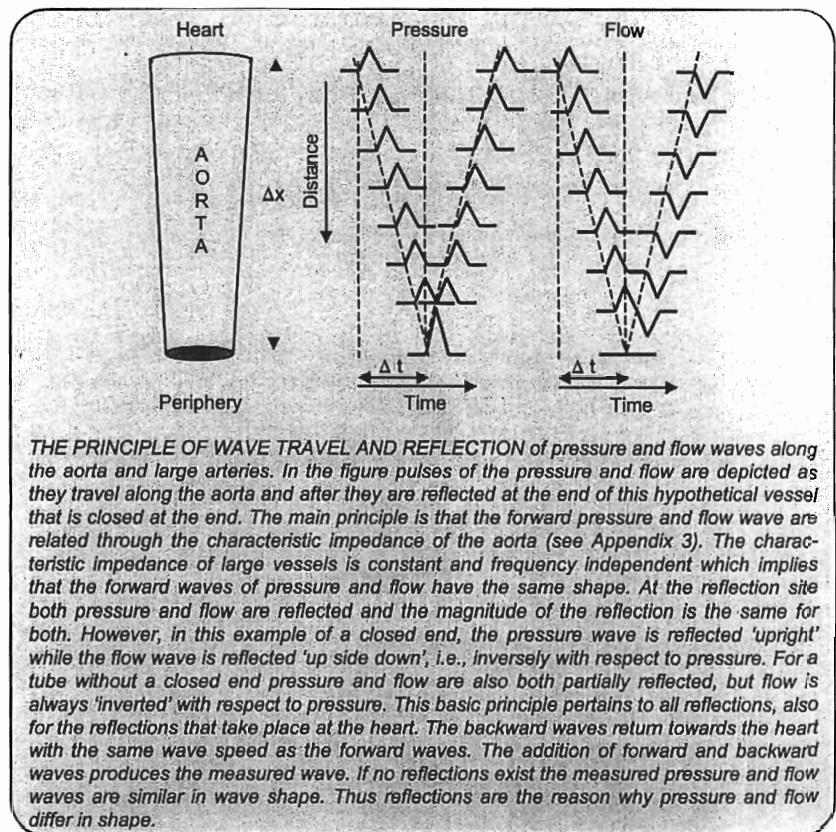


PULSE WAVE VELOCITY of the aorta as a function of age in individuals with low prevalence of atherosclerosis in Beijing. From [1], used by permission.

of cardiovascular mortality and morbidity than systolic blood pressure [5].

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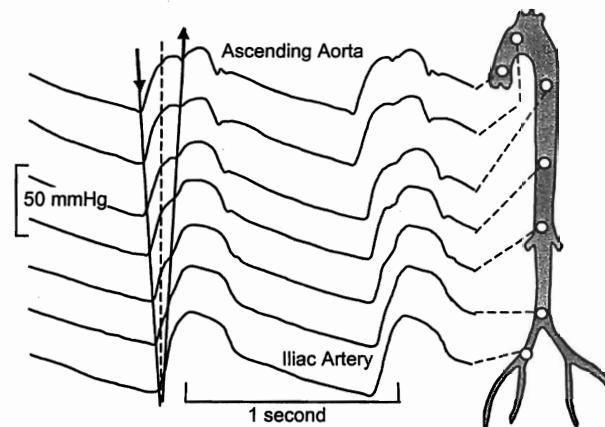


### Description

Wave reflection takes place at all bifurcations and discontinuities of the vasculature. However, it turns out that the major reflections occur at the arterioles, i.e., in the periphery where many bifurcations are present over short distances. This leads to diffuse reflection. In addition, especially in the human, there appears to be a distinct reflection site in the distal abdominal aorta. An example of the distinct reflection is shown in this figure. The moment the reflected waves return at the heart depends on the length of the system and the wave speed. Since with age the wave speed increases, the reflections will return earlier in older subjects. The example is that of an older, healthy, person [1].

The amount of reflection is given by the reflection coefficient, which is defined for sinusoidal waves, as the ratio of the backward and forward waves and consists of a modulus or magnitude, and phase angle. Calculation of the reflection coefficient requires Fourier analysis because the coefficient is different for each harmonic (Appendix 1). The modulus of the reflection

coefficient is the same for pressure and flow but the phase angle of pressu



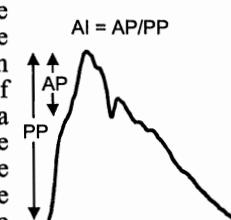
**SIMULTANEOUSLY MEASURED PRESSURES IN THE HUMAN AORTA.** The foot of the wave arrives later in the periphery and the reflected wave (inclination point) returns to the heart. The points are connected to show the later arrival at the heart compared to the distal aorta. The ECG is plotted at top and bottom to emphasize the time delays. Adapted from [1], used by permission.

and flow differ by 180 degrees ('up side down'). Calculation of the reflection coefficient therefore requires Fourier analysis of the forward and backward (Chapters 21 & 22) pressure waves, as in the impedance calculations. In approximation, the ratio of the amplitudes of backward and forward waves can be used as a measure of the magnitude of reflection, usually in the form of the Reflection Index (see Chapter 22). The magnitude of the reflected wave with respect to the forward wave is related to the magnitude of the oscillation of the modulus of the input impedance (see Chapter 23).

The amount of reflection has also been related to the Augmentation Index, AI. The Augmentation Index became very popular, in part because it can be determined noninvasively and calibration of the signal is not required so that, for instance, applanation tonometry can be used. However, the Augmentation Index depends not only on the magnitude of the reflected wave but also on the time of return.

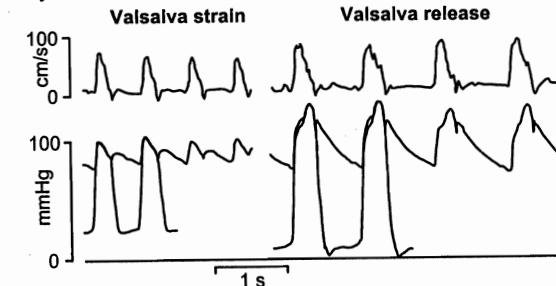
#### Physiological and clinical relevance

The amount of diffuse reflection depends on the vasoactive state of the peripheral vascular bed. With increased vasoconstriction the so-called diffuse reflections increase as well and pressure and flow become less alike in shape. For examples see below, and also Chapters 22 and 14. Inversely, during vasodilation pressure and flow in the aorta become more alike: a pressure



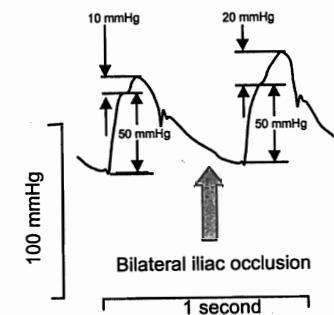
**THE AUGMENTATION INDEX (AI)** is the augmented pressure (AP) divided by pulse pressure (PP). Calibration of blood pressure is not required.

wave with an early peak, akin to the flow wave shape, is found in patients with a severely dilated state. With the Valsalva maneuver the transmural



**DURING THE VALSALVA** strain pressure and flow in systole become alike because diffuse reflections decrease in amplitude and wave speed decreases so that reflections return in diastole. After the release reflections return in systole. Adapted from [2], used by permission.

pressure in thoracic and abdominal aorta decreases [2]. This results in a more compliant aorta and a lower wave speed. The diffuse reflections decrease in magnitude and the reflected wave from the distinct reflection site arrives later in diastole. The overall result is that reflections that return in systole are negligible leading to a very similar shape of aortic pressure and flow in systole.



**DISTINCT REFLECTION** in the ascending aortic pressure is increased by mechanical compression of both iliac arteries. Adapted from [1], used by permission.

An experiment where the distinct reflection is increased is shown in the figure above. When both iliac arteries are manually occluded, the distinct reflection coefficient increases and the backward wave is increased resulting in a large Augmentation Index.

In hypertension, wave speed is increased. Resistance and thus diffuse reflections are also increased. This results in a large reflected wave in systole, adding to the forward wave resulting a large Augmentation Index, and in higher systolic pressure.

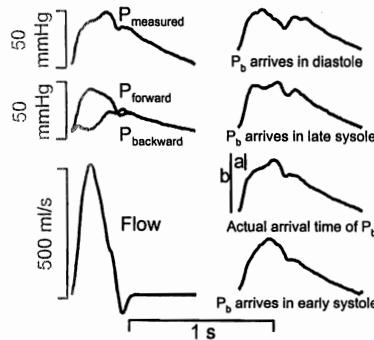
With increased reflection, and thus a higher Augmentation Index, the so-called supply-demand ratio of the cardiac muscle is negatively affected (see Chapter 16).

Not only the magnitude of the reflected wave but also the time of return is of importance. The moment the reflected wave returns in the ascending aorta depends on the wave speed and the distance between the reflection site and the heart. Thus the Augmentation Index does not only depend on the magnitude of reflection but it is affected by the moment the reflected waves return (see figure on next page). Therefore estimation of the magnitude of the reflections cannot be done solely based on the Augmentation Index.

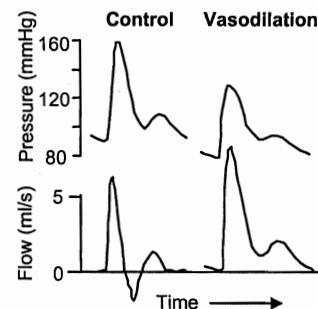
Reflection in the periphery causes a backward flow wave that may be seen as a reversal of the measured flow wave, figure below right. This negative part of the flow wave is greatly reduced in vasodilation, when the reflection and thus the backward flow wave is smaller. Also, mean flow is larger, and the measured flow wave does not exhibit a reversal.

The distance between heart and the major reflection site has been called the effective length of the arterial system. However, the derivation of the effective length from the travel times of forward and backward waves is subject to errors because at the reflection site the reflected wave may be shifted in phase. This phase shift introduces time delay. From measurements of the time of arrival of the reflected wave in the proximal aorta it is not

possible to distinguish between times resulting from travel per se and the phase shift [5]. Pythoud et al. have suggested a possible solution [4]. See also the Chapter 23.



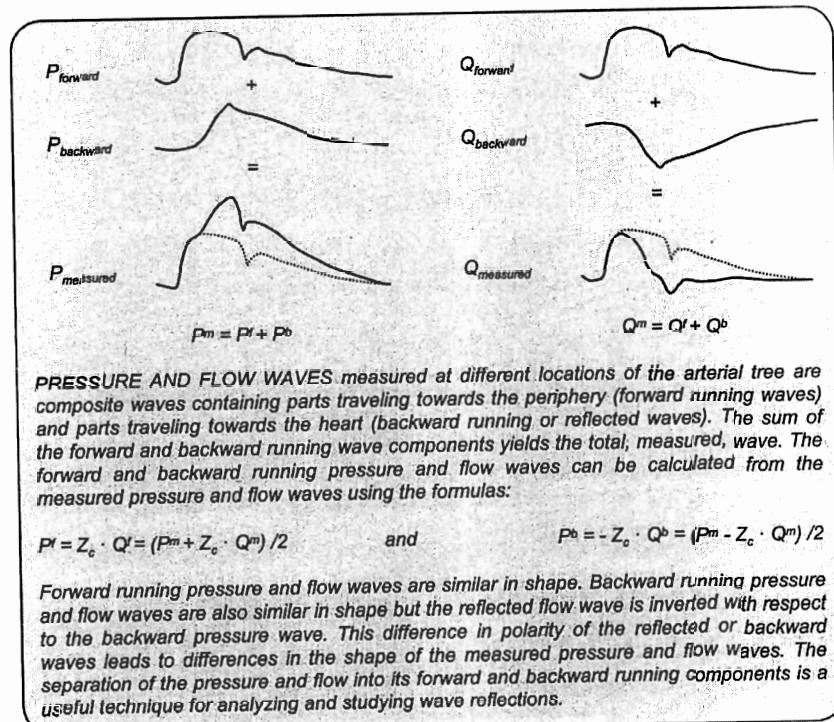
THE AUGMENTATION INDEX, a/b, depends on the magnitude of reflection and time of return of the reflections. The pressure wave is separated into its forward and backward components (left). The backward wave is then shifted in time and the summated wave is calculated. It may be seen that the augmentation index strongly depends on the time of return of the reflected wave (right).



NEGATIVE BLOOD FLOW in part of the cardiac cycle results from inertia and reflections. With vasodilation the reflections decrease and flow reversal disappears (femoral artery). Adapted from [3], used by permission.

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## Description

At any location in the arterial tree, the measured pressure and flow waves are the sum of waves traveling from the heart towards the periphery (forward running waves) and waves traveling from peripheral arteries towards the heart (backward running waves). The backward running waves are often called reflected waves, simply because they arise from reflections of the forward running waves at arterial reflection sites.

### Separation of waves into their forward and backward running components

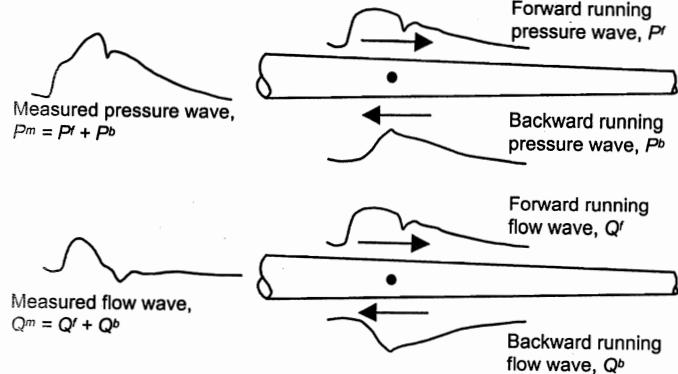
Consider the schematic diagram given on the next page. As mentioned above, at any arterial location the measured pressure and flow waves (shown on the left) are the sum of their forward and backward running components. So, we may write

$$P^m = P^f + P^b$$

and

$$Q^m = Q^f + Q^b$$

## Arterial Hemodynamics



**PRINCIPLE OF THE SEPARATION** of pressure and flow waves into their forward and backward running components.

The forward running flow wave and the forward running pressure wave, are related through the relation,  $P^f = Z_c \cdot Q^f$ , with  $Z_c$  the local characteristic impedance of the vessel (for the definition of  $Z_c$  see Appendix 3). The reflected flow and the reflected pressure wave are also related by the characteristic impedance,  $P^b = -Z_c \cdot Q^b$ . The minus sign results from the fact that flow, compared with pressure, is reflected 'up side down' (Chapter 21). Substituting  $Q^f$  and  $Q^b$  into the above equations we obtain:

$$P^f = Z_c \cdot Q^f = (P^m + Z_c \cdot Q^m)/2$$

and

$$P^b = -Z_c \cdot Q^b = (P^m - Z_c \cdot Q^m)/2$$

The above formulas are simple to use when the characteristic impedance,  $Z_c$ , is a real number, which means that we neglect the blood viscosity and the viscoelasticity of the wall. This is often a good approximation, especially when referring to conduit arteries, in which case we may calculate  $Z_c$  as:

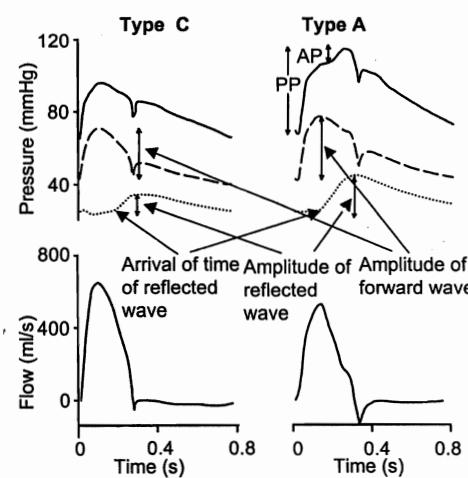
$$Z_c = \rho \cdot c / A$$

with  $\rho$  blood density,  $c$  the local pulse wave velocity and  $A$  the luminal cross-sectional area. If, however, wall friction and viscoelasticity cannot be neglected, as in smaller vessels, then the same analysis holds and same equations apply, with the exception that the characteristic impedance  $Z_c$  is a complex number. In this case the analysis should be done in the frequency domain. This implies Fourier analysis (Appendix 1) of the measured pressure and flow waves, application of the above relations for each harmonic and inverse Fourier to reconstruct the time functions of the waves.

Another approach to the analysis of pressure and flow in a given arterial location is to look at very small portions of the traveling wave ( $dP$  or  $dQ$ ). This is called wave intensity analysis [1]. The application of 'wavelets' to separate the pressure and flows into their forward and backward running components leads to identical results when compared to the method expressed by the equations given above.

## Waveform Analysis

## Physiological and clinical relevance



**ANALYSIS OF AORTIC PRESSURE WAVES** (fully drawn) into their forward (dashed lines) and reflected, or backward, waves (dotted lines). The Type C beat pertains to a young healthy adult and the Type A beat to an older subject.

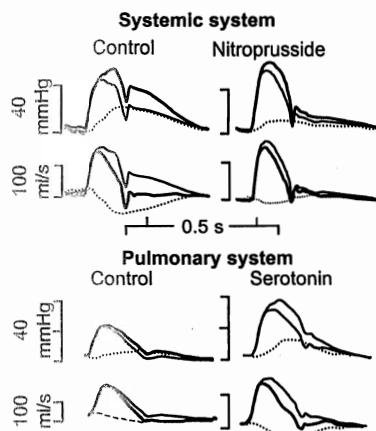
systole. The net effect is that the addition of the reflected wave onto the forward wave does not lead to a significant increase in late systolic pressure. In contrast, in the old subject, we observe considerably higher amplitude of the reflected wave, which also arrives early in systole. Here the addition of the reflected wave to the forward wave leads to a very pronounced late systolic peak, resulting in a considerable increase in systolic pressure. The late systolic peak in the Type A beat results from wave reflection (Chapter 21) and has been related to the Augmentation Index, AI, defined as the ratio  $AP/PP$ . The limitation of the AI has been discussed in Chapter 21. The wave separation technique presented here is a better way for the quantification of reflection, and account for the timing, amplitude, and shape of the reflected waves.

## Practical determination of characteristic impedance

In practice, the characteristic impedance of large vessels can be determined in two ways. The first is by averaging of the modulus of the input impedance between the 4th and tenth harmonic (Chapter 23). The second method is by taking the slopes of the aortic pressure and flow waves during the early part of the ejection phase,  $\Delta P$  and  $\Delta Q$ , and calculating their ratio:  $Z_c = (\Delta P/\Delta t)/(\Delta Q/\Delta t)$  [2]. Both methods rely on the fact that characteristic impedance is a pressure flow relation in the absence of reflections. Reflections are small in early systole and at high frequencies (see Chapter 23).

The analysis of arterial pressure and flow waves into their forward and backward running components can be used to quantify the role of wave reflections in certain physiological and pathological situations. The figure shows the aortic pressure and flow waves measured in young healthy adult, type C beat, and an older subject, type A beat [3]. The figure also shows the forward and backward running pressure components as dashed and dotted lines, respectively. For the type C beat we observe that the amplitude of the reflected wave is rather small and in the order of 12 mmHg. Further, the rise in the reflected wave takes place relatively late in

Reflections depend on the vascular bed and on its vasoactive state.



Wave reflections in the pulmonary circulation are less significant than in the systemic arterial tree [4]. Aortic pressure and flow and common pulmonary artery pressure and flow, are broken down in their forward and backward components. When the systemic bed is dilated, with nitroprusside, and the pulmonary arterial system is constricted, with serotonin, reflections decrease and increase, respectively. It should be noticed that when reflections are small in magnitude, the pressure and flow waves become similar in shape.

#### Reflection Index

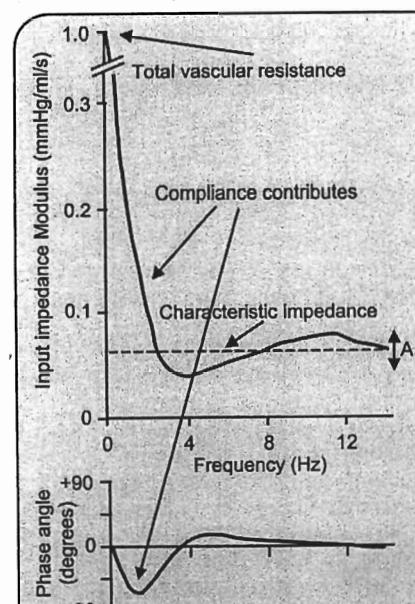
PRESSURE AND FLOW in aorta and common pulmonary artery are broken down in their forward and backward components. Thick lines, thin lines, and dashed lines give measured waves, forward waves, and backward waves, respectively. With vasodilation and vasoconstriction backward waves are reduced and increased, respectively. Adapted from [4], used by permission.

#### Augmentation Index and shape of the waves

The Augmentation Index, AI, is derived from the measured pressure wave without the need for application of wave separation. However, while the Reflection Index, gives a good measure of the magnitude of (total) reflection, the Augmentation Index is determined by both the delay and the shapes of the forward and backward waves. In Chapter 21 it was shown that for the same magnitude and wave shape of the backward and forward waves the delay between them strongly determines Augmentation Index.

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INPUT IMPEDANCE COMPLETELY AND COMPREHENSIVELY DESCRIBES AN ARTERIAL SYSTEM. Here the input impedance of the human systemic arterial tree is shown. The ratio of the mean arterio-venous pressure drop and mean flow is total vascular resistance or peripheral resistance. To obtain information about the oscillatory aspects of the arterial system wave shapes of pressure and flow are used. To derive this information sinusoidal pressures and flows as obtained by Fourier analysis are related. The amplitude ratio and the phase difference of the sine waves of pressure and flow are calculated, giving the modulus and phase angle of the impedance (application of Ohm's law). The impedance modulus and phase are plotted as a function of the frequency: at zero frequency is the systemic vascular resistance. For intermediate frequencies the modulus decreases precipitously and the phase angle is negative. This shows the contribution of arterial compliance. For high frequencies the modulus approaches a constant value and the phase angle is close to zero. This is the contribution of the aortic characteristic impedance, which is a real quantity for large vessels. Thus the three-element windkessel gives a good description of the input impedance and its parameters are indicated in the figure. Without reflections in the arterial system, the input impedance would equal aortic characteristic impedance and the pressure and flow would have the same wave shape. For low frequencies the reflections at the periphery, 'diffuse reflections' are large and cause the impedance to be high. At high frequencies local, 'distinct reflections' play a role and they determine the oscillations in the impedance about the characteristic impedance. The oscillations about the characteristic impedance are related to the Augmentation Index, A.I. The frequency of the minimum in the impedance modulus and the zero crossing of the phase angle have been used to calculate the effective reflection site (the quarter wave length rule). This calculation is often inaccurate. Input impedance can be derived for any (sub) section of the arterial system, but the present chapter mainly concentrates on the systemic arterial system as a whole.

#### Description

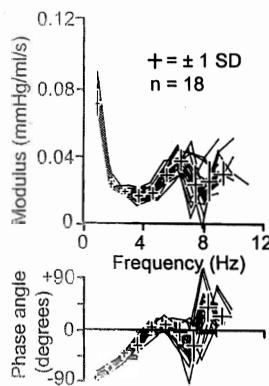
##### Definition of impedance

Impedance is the relation between the pressure difference and flow of a linear system, for sinusoidal or oscillatory signals. Impedance completely describes the system and it can be derived from pulsatile pressure difference and pulsatile flow and the application of Fourier Analysis. Inversely, when the impedance is known, a given flow allows for the calculation of pressure and vice versa. Systemic arterial and pulmonary arterial input impedance are a comprehensive description of the systemic and pulmonary arterial tree. Input

impedances of organ systems may be derived as well. The longitudinal, transverse and characteristic impedance are discussed in Appendix 3.

#### Derivation of input impedance

In the calculations of input impedance we use both the mean values and the pulsatile part of the pressure and flow. We apply Fourier analysis of the aortic pressure and flow because the calculations are based on sinusoidal signals. The details and limitations of Fourier analysis are discussed in Appendix 1. To derive impedance Ohm's law is applied. For each pair of sine waves of pressure and flow we calculate the ratio of the amplitudes and the phase angle difference between them. To apply Ohm's law, i.e., to calculate impedance and vascular resistance, the system must be in the steady state, time-invariant, and linear. This means that the arterial system may not vary in time, e.g., vasoconstrictor tone should be constant, that the relation between pressure and flow is a straight line, e.g., if a sine wave of pressure is applied a sine wave of flow should result. For a time-varying system the calculation of impedance does not lead to interpretable results. The coronary circulation, where resistance and elasticity vary over the heartbeat, the calculation of impedance from pressure and flow using Fourier analysis is not sensible. For a nonlinear system the calculation of impedance also does not lead to interpretable results. An example is the calculation of 'impedance' from ventricular pressure and aortic flow, where the aortic valves make the system nonlinear. The arterial system is not perfectly linear but the variations of pressure and flow over the heartbeat are sufficiently small so that linearity is approximated and the derived impedance is a meaningful description. It has been shown that some of the scatter of the input impedance data results from nonlinearity [7].



**SCATTER IN THE INPUT IMPEDANCE** is caused, in part, by noise on the pressure and flow signals especially affecting the small amplitudes high harmonics. Non-linearity of the arterial system also contributes to the scatter. From [1], used by permission.

averaging the results. This can be done by using, for instance, an entire

These limitations in the calculations of input impedance also hold for the calculation of peripheral resistance. Mean aortic pressure divided by mean aortic flow only gives information on peripheral resistance if, over the period of determination, the peripheral resistance does not vary. Also, mean left ventricular pressure over mean aortic flow does not lead to a sensible result because the system includes the valves and is not linear.

Fourier analysis and subsequent calculation of the input impedance only gives information at frequencies that are multiples of the heart rate, i.e., harmonics. By pacing the heart at different rates, the frequency resolution can be increased.

Because the information contained in the signals for high frequencies is small, the higher harmonics (Appendix 1) are subject to noise, so that the impedance at high frequencies often scatters considerably. This limitation can be partly circumvented by analyzing more than one heartbeat and

respiratory cycle (steady state of oscillation) or by analyzing a series of beats individually followed by averaging [1].

In the systemic circulation venous pressure may be neglected (Chapter 6), so that the use and Fourier analysis of aortic pressure and flow gives a sufficiently accurate approximation of the input impedance. However, in the analysis of the pulmonary circulation venous pressure cannot be neglected.

In Appendix 2 the basic hemodynamic elements are discussed. For a resistor it holds that the sine waves of pressure and flow are in phase, i.e., the phase angle is zero. For compliance the flow is advanced with respect to pressure. This is seen as -90 degrees in the impedance phase angle. For inertance flow is delayed, and shows as +90 degrees for the impedance phase. The modulus of the impedance decreases with frequency,  $1/\omega C$  for compliance, and increases with frequency,  $\omega L$ , for the inertance, respectively. In Appendix 3 it is shown that in the case of the characteristic impedance of a large artery, like the aorta, the mass effects and compliance effects interact in such a way that sinusoidal pressure and flow waves are in phase, and their ratio is constant. Thus the impedance phase angle is zero and the modulus is constant and independent of frequency. This means that the amplitude ratio of pressure and flow is the same for all frequencies and the phase angle is zero. Thus for large vessels the characteristic impedance is similar to a resistance and is often called characteristic resistance, and modeled as a resistor. However, characteristic impedance is non-existent at zero Herz and no energy is lost in it. Thus when modeling characteristic impedance with a resistor these limitations must be kept in mind.

#### Explanation of input impedance

**The Windkessel.** The qualitative description of the impedance given in the box refers to the Windkessel model. The original two-element Windkessel, proposed by Frank, consists of peripheral resistance,  $R_p$ , and total arterial compliance,  $C$ . From the information on input impedance, which became available in the 1960s, the idea of aortic characteristic impedance,  $Z_c$ , appeared [10]. However, we should keep in mind that when the characteristic impedance is modeled with a resistor the mean pressure over mean flow will be  $R_p + R_c$ , while it should be  $R_p$  only. Although this error is not large for the systemic circulation where  $R_c$  is about 7% of  $R_p$ , it leads to errors when, for instance the three-element Windkessel is used to estimate total arterial compliance. To correct for these shortcomings, a fourth element, the total arterial inertance (see Chapter 24) was introduced [6].

**Wave transmission.** From wave transmission we can explain the impedance as follows. For a reflectionless system the input impedance equals aortic characteristic impedance and, inversely, the difference between input impedance and characteristic impedance results from reflections. For low frequencies the reflections from bifurcating arteries and other discontinuities mainly from the periphery, where bifurcations occur over short distances, return to the proximal aorta resulting in an impedance that strongly differs from aortic characteristic impedance. For high frequencies, where wavelengths are less than the length of the arterial system, the waves return out of phase, and cancel each other out so that the arterial system appears reflectionless. Also damping is stronger for the high frequencies. For high frequencies input impedance is, therefore, close to the characteristic impedance and its phase angle is close to zero. The (small) oscillations of the

impedance modulus around the characteristic impedance, and the oscillations in phase angle, result from reflections relatively close to the heart. It has been suggested that in the human these reflections may occur at the aortic bifurcation or at the level of the renal arteries. This is considered a distinct reflection site. The ratio of backward and forward running wave amplitudes is related to the magnitude of the oscillations in the impedance modulus [1].

#### *Effective length of the arterial system*

The effective length of the arterial system is used as a conceptual description to determine at what distance from the ascending aorta the major reflections arise. In this concept it is assumed that the arterial system behaves like a single tube, the aorta, with a single resistance, the peripheral resistance at its distal end. To derive the effective length it is assumed that the arterial system can be modeled by a single tube, the aorta, loaded with a resistance, peripheral resistance. Since the aortic characteristic impedance is a real number (no phase angle), the reflection coefficient is real as well. Let us consider a sinusoidal pressure and flow, with a wavelength 4 times the length of the aorta. When the forward pressure wave travels a quarter wave length to reach the end of the tube, and again one quarter wave length to return at the heart, the forward and reflected waves of pressure are 180 degrees out of phase and thus cancel. Thus the measured pressure wave is negligible. For the flow waves the same holds, but the flow waves are reflected 180 degrees out of phase (Chapter 21). Thus the forward and reflected flow waves are 360 degrees out of phase: 180 degrees results from the reflection and the other 180 degrees results from traveling half a wavelength. This means that forward and backward flow waves are in phase and the measured flow about twice the forward or backward wave. Thus for a frequency where this model system is a quarter of a wavelength long, pressure is negligible, and flow is large, and the modulus of the input impedance is small and the phase angle is zero. This is called the quarter wavelength principle.

Quantitatively we describe this phenomenon as follows. The wave speed,  $c$ , equals wavelength,  $\lambda$ , times frequency,  $f$ , thus,  $c = \lambda \cdot f$ . When the length of the tube is a quarter wave length,  $l = \lambda/4$ , and the minimum of the impedance is found at frequency  $f = c/l = c/4\lambda$  or  $l = c/4f$ . With a wave speed in the aorta of 6 m/s and the frequency of the minimum in the impedance modulus or zero crossing of the phase at 4 Hz, the effective length equals ~38 cm. However, the assumption of a single tube, loaded with the peripheral resistance as model of the systemic arterial tree, is too simple and often unrealistic. When the reflection coefficient is not real, i.e., when the phase of the pressure and flow waves are changed at the reflection site, the calculation may even lead to an effective length longer than the arterial system [4]. When the impedance modulus minimum and zero crossing of the phase angle are not at the same frequency, the assumption that the arterial system can be modeled with a single tube and a peripheral resistance is violated.

#### *Impulse response*

Conceptually, it is rather awkward that while pressure and flow are functions of time, the input impedance is expressed as a function of frequency. There exists a characterization of the arterial system in the time domain. This characterization is the so-called impulse response function, which is the pressure that results from an impulse of flow, i.e., a short lasting flow, short

with respect to all travel and characteristic times of the arterial system, typically about 1-5 ms of duration. Because the impulse has a height with dimension ml/s and the duration is in seconds, the area under the impulse is ml. The pressure response resulting from this impulse is normalized with respect to the volume of the impulse and the units of the impulse response are therefore mmHg/ml. The calculation of the impulse response function from measured pressure and flow is complicated but straightforward [5]. When the measured flow is broken up in a number of short impulses, the proper addition of the impulse responses leads to the pressure as a function of time.

The input impedance and impulse response function are a 'Fourier pair'. Fourier analysis of the impulse response function leads to the input impedance and inverse transformation of input impedance leads to the impulse response function [5].

If the impulse response is short in duration with respect to the time constant of variation of the time varying system, it may be used to obtain a characterization of that system as a function of time. For example, if the duration of the impulse is a few milliseconds, and the system under study varies with a typical time of a few hundred milliseconds, the system can be characterized by the impulse response. In this way input impedance of the coronary arterial system was derived in systole and diastole [8].

#### **Physiological and clinical relevance**

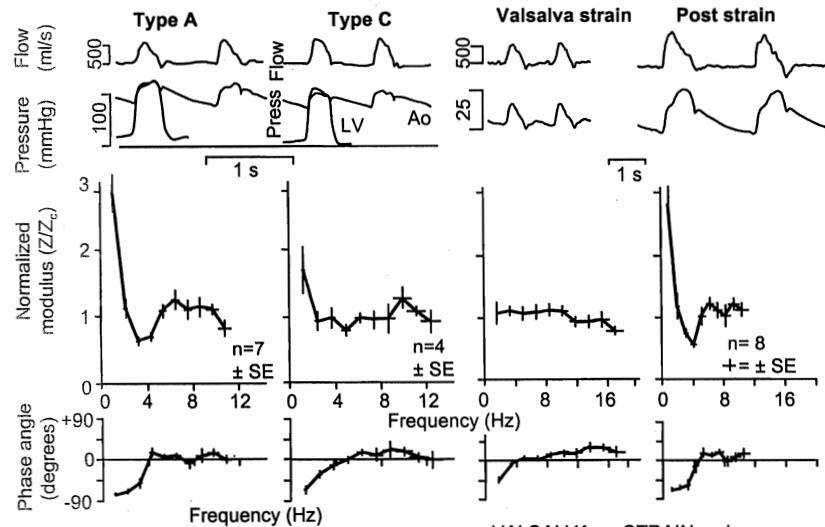
As discussed above, derivation of input impedance requires sophisticated analysis of pressure and flow waves. Thus, routine clinical applications are seldom carried out. However, impedances calculated in the human and mammals have led to a much better understanding of arterial function. For instance, the three-element Windkessel as an extension of the two-element Windkessel of Frank could only be proposed after input impedance data became available. It has also been shown that the input impedance of different mammals, when normalized, is similar [9]. This explains, in part, why aortic pressures and flows are so similar in shape in all mammals (Chapter 30).

The arterial system can be described in terms of Windkessel models and distributed models. The main arterial parameters describing input impedance are peripheral resistance, total arterial compliance and aortic characteristic impedance. Recently the total arterial inertance has been suggested as the fourth element of the Windkessel [6]. It is often easier and more accurate to determine the windkessel parameters to describe the arterial system. With the modern computing techniques the calculation of the three or four parameters of the Windkessel model can be performed rapidly and gives directly interpretable results. For instance, a change in total arterial compliance can thus be obtained directly, while the impedance calculations can be avoided.

In terms of distributed models the pressure and flow waves can be better analyzed in terms of forward and backward running waves than in terms of impedance (Chapter 22). The amplitude ratio of the backward and forward waves appears to relate with the oscillations of the modulus of the impedance around the characteristic impedance. The time of arrival of the backward wave gives a better estimate of the effective length of the arterial system than the minimum in the impedance modulus or zero crossing of the phase angle.

## Arterial Hemodynamics

The following examples show that, although the pressure and flow waves result from the interaction of the heart and arterial load, major features of the pressure wave shape arise from the arterial system and can therefore be related to aspects of the input impedance.



**TYPES OF BEATS RELATE TO INPUT IMPEDANCE.** In older subjects, Type A, with high pulse wave velocity, reflections return in systole and augment the pressure wave. The impedance oscillates about the characteristic impedance. In young subjects, Type C, reflections are smaller and return in diastole. The impedance oscillates less. Adapted from [1], used by permission.

**VALSALVA STRAIN** increases thoracic and abdominal pressures. The lower transmural pressure increases arterial compliance and lowers pulse wave velocity. Reflections diminish and return later, in diastole. An almost reflectionless situation appears where pressure and flow resemble each other and input impedance equals aortic characteristic impedance. In the release phase the reverse is true, reflections return in systole and are large. Adapted from [2], used by permission.

### The characteristic pressure wave shapes in old and young subjects

In older subjects, where arterial compliance is decreased and pulse wave velocity is increased (Chapter 20), the reflected waves return earlier in the cardiac cycle and thus arrive back in the ascending aorta during systole. The reflected waves add to the forward pressure wave resulting in a secondary increase in systolic pressure, a Type A wave (Chapter 22). The secondary increase in pressure relative to pulse pressure is called the Augmentation Index, AI. The AI is clearly seen in a so-called Type A beat. As a result of the strong reflection the input impedance oscillates around the characteristic impedance. In young subjects with small reflections that return in diastole due to the low pulse wave velocity, the pressure shows an early maximum,

## Arterial Input Impedance

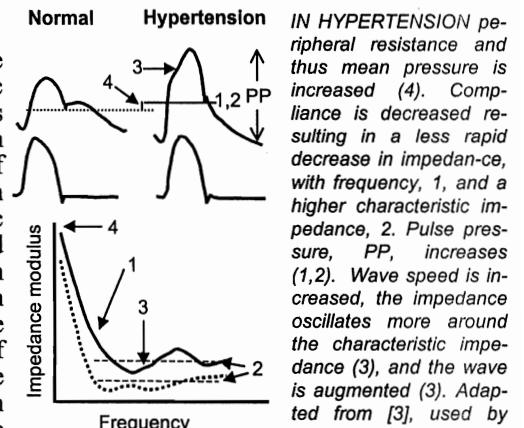
with negligible or negative augmentation, and the impedance oscillates only little.

### Changes in reflection

In the figure on the right we see that during the Valsalva maneuver aortic pressure resembles aortic flow in wave shape [2]. During the Valsalva maneuver intra-thoracic and intra-abdominal pressures increase. The transmural pressure of the aorta decreases and the compliance increases leading to a decreased pulse wave velocity. As a result reflections return slower and arrive late in the cardiac cycle, in diastole. Reflections are probably also decreased in magnitude. The result is an almost reflectionless arterial system. Pressure and flow become similar in shape and the input impedance is close to the characteristic impedance of the aorta (Figure on previous page). After the release of the Valsalva maneuver, cardiac filling and transmural pressure are increased, Cardiac Output and pulse wave velocity are increased as well and reflections return in systole, and a large augmentation in the pressure is seen.

### Hypertension

In the figure below we see the relation between systolic hypertension and the changes in the arterial system presented in the form of input impedance. With increasing age systolic pressure increases and diastolic pressure even decreases what. The main age-related change in the arterial system is decrease of arterial compliance. The decrease in compliance can be seen in the impedance graph: the modulus decreases less rapidly with increasing frequency (1) and the characteristic impedance is increased (2). The pulse wave velocity is also increased and therefore the waves reflected at the level of the lower abdominal aorta return earlier at the heart and augment the pressure wave in the ascending aorta. The result is larger oscillations of the impedance around the characteristic impedance and a larger pulse pressure (3). Peripheral resistance also increases somewhat and the result is a small increase in mean pressure (4).



**IN HYPERTENSION** peripheral resistance and thus mean pressure is increased (4). Compliance is decreased resulting in a less rapid decrease in impedance, with frequency, 1, and a higher characteristic impedance, 2. Pulse pressure, PP, increases (1,2). Wave speed is increased, the impedance oscillates more around the characteristic impedance (3), and the wave is augmented (3). Adapted from [3], used by permission.

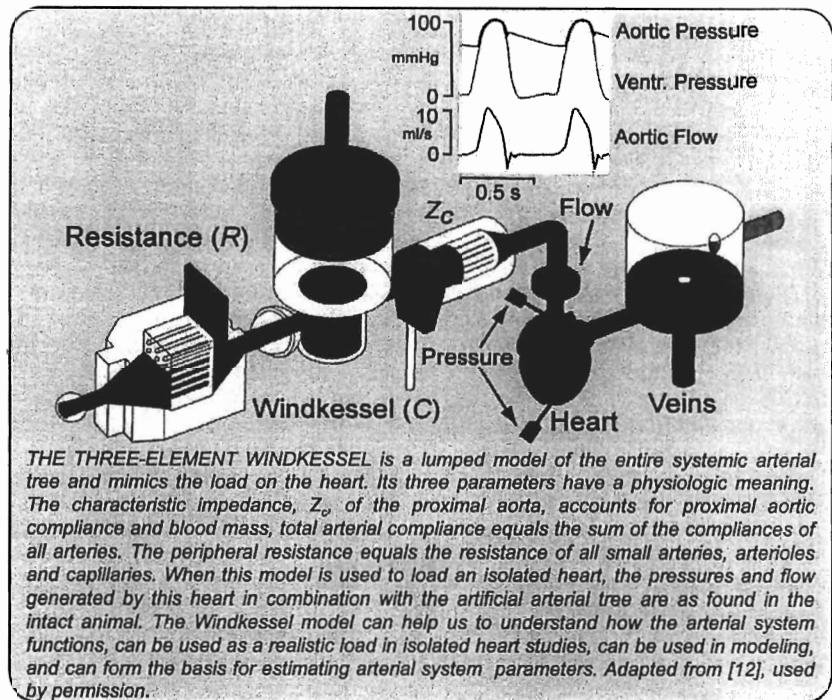
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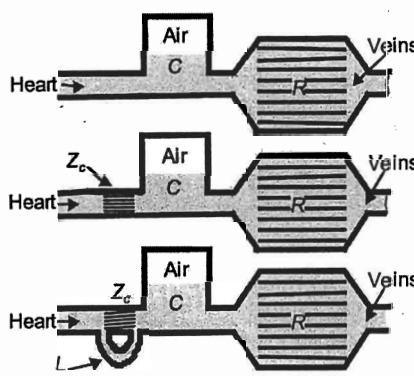
## Chapter 24

### ARTERIAL WINDKESSEL



### Description

Three Windkessel models are given in the figure. Otto Frank, 1899, popularized the original two-element Windkessel. He reasoned that the decay



**THE THREE WINDKESSELS.** The two-element windkessel (Frank) contains total peripheral resistance, mainly located in the arterioles (R), and the total arterial compliance (C), accounting for elasticity of all arteries, with the major contribution of the large conduit vessels. The three-element windkessel contains the aortic characteristic impedance, accounting for the combined effects of compliance and inertance of the very proximal aorta, and forming a link with transmission line models. The four-element windkessel contains total arterial inertance, playing a role at the very low frequencies. It also solves the problem that characteristic impedance, although having the dimension of a resistor, is not a real resistor and therefore mean pressure over mean flow equals  $Z_c + R$  in the three-element windkessel.

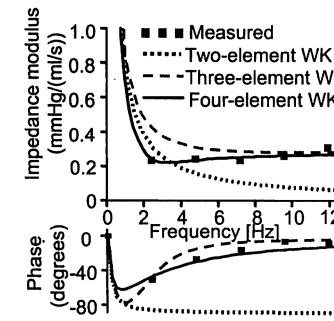
of diastolic pressure in the ascending aorta, when flow is zero, can be described by an exponential curve. The time constant,  $\tau$ , i.e., the time for pressure to decrease to 37% of the starting pressure, is given by the product of peripheral resistance,  $R$ , and the total arterial compliance,  $C$ ,  $\tau = RC$ . The larger the resistance the slower the blood, stored in the compliant conduit vessels, leaves the system and the longer the time constant will be. Also, the larger the compliance the more blood is stored, and the longer the time constant will be. Frank's objective was to derive Cardiac Output from aortic pressure. By measuring the pulse wave velocity over the aorta (carotid to femoral) together with, averaged, cross-sectional area, and using the Moens-Korteweg equation (Chapter 20) area compliance,  $C_A$ , can be estimated. When aortic length is also known volume compliance,  $C$ , is derived. Using  $\tau$  and  $C$ , the peripheral resistance can be calculated from  $R = \tau/C$ . From mean pressure and resistance, using Ohm's law, mean flow is then found. The assumption that all compliance is located in the aorta, thus neglecting the compliance of the smaller conduit vessels, introduces a small error. Only after pulsatile flows could be measured, and the arterial input impedance could be determined (Chapter 23), the shortcomings of the two-element Windkessel became clear.

The three-element Windkessel is based on Frank's two-element Windkessel with the addition of the characteristic impedance [12]. Input impedance shows, at high frequencies, a constant impedance modulus and a phase angle of about zero degrees (Chapter 23). This is not in line with the impedance of the two-element Windkessel that exhibits a continuously decreasing modulus and a phase angle that approaches minus 90 degrees for high frequencies. From a wave transmission and reflection standpoint, it can be reasoned that for high frequencies reflections in the proximal aorta cancel out and for a reflectionless aorta the input impedance equals its characteristic impedance (Chapter 22). Or, in other words, for high frequencies the input impedance equals the characteristic impedance of the proximal aorta. Aortic characteristic impedance is a real number, i.e., its modulus is constant with a value  $Z_c = \sqrt{\rho \cdot \Delta P / (\Delta A \cdot A)}$  and its phase angle is zero (Appendix 3). This behavior is also characteristic of a resistance. Therefore, a resistor has often been used to mimic the characteristic impedance of the proximal aorta. The introduction of the characteristic impedance or characteristic resistance as the third element of the Windkessel can be seen as bridging the lumped models and the transmission line models. However, the characteristic impedance is only present for oscillatory pressure and flow (Chapter 23).

The approximation of characteristic impedance by a resistor leads to errors in the low frequency range. When, for instance, total arterial compliance is determined from aortic pressure and flow by parameter estimation of the three elements of the Windkessel, the compliance is consistently overestimated. The reason is that the decrease of the impedance modulus and the negative phase angles at low frequencies are mainly determined by compliance.

The fourth element of the Windkessel was introduced to circumvent the inconsistency resulting from modeling the characteristic impedance by a resistance [8]. The four-element Windkessel is also shown in the figure on the previous page. It has been established that the inertance term equals total inertance of the arterial system. Using this four-element Windkessel model, total arterial compliance is estimated accurately from pressure and flow.

In summary, the characteristic impedance introduces transmission concepts into the Windkessel model and provides for a correct behavior of the model at high frequencies. The total arterial inertance improves the very low frequency behavior of the Windkessel.



THE INPUT IMPEDANCES of the two-element, three-element and four-element windkessel models. The squares give the measured input impedance. The two-element Windkessel clearly falls short, especially in the high frequency range. The three-element Windkessel is also less accurate at very low frequencies. This is the result of the representation of the characteristic impedance by a resistance. The four-element Windkessel solves this problem. The  $R$ ,  $C$ , and  $L$  represent total arterial resistance, compliance and inertance. Adapted from [8], used by permission

When flow is zero, as in diastole, the decrease of aortic pressure, is characterized by the decay time, which equals  $RC$  for all three Windkessel models, if the analysis is started with some delay after valve closure (about 10% of the heart period).

These lumped models only mimic the behavior of the entire arterial system at its entrance. The input impedances of the Windkessels are given in the figure above. The integrated description of the entire arterial system means that pressures within these models have little meaning. The measurement of pressure distal of the characteristic impedance, for instance, does not represent the pressure in the more distal vascular system.

#### Other lumped models

Other lumped models are partly Windkessel models with more elements and partly tube models. More elements in the Windkessel may evolve to transmission line models, but often the parameters lose their physiologic meaning. Tube models consist of single tubes, loaded with a resistor or with a Windkessel model. Two tube models may consist of two tubes in parallel or in series (Chapter 25). Wave transmission, not existing in the Windkessel models, is present in the tube models, which gives them certain advantages.

#### Physiological and clinical relevance

Windkessel models find their use as load for the isolated ejecting heart. The Windkessel parameters may be changed and cardiac pump function studied [1]. The figure on the next page shows an example of changes in peripheral resistance and total arterial compliance while cardiac contractility, heart rate and cardiac filling are maintained constant.

Another use of the Windkessel models is the estimation of arterial parameters. Several methods have been proposed to derive total arterial compliance [9]. These methods are:

- The decay time method described above.

- The *Stroke volume over Pulse Pressure method*. This method is rather old but has been reintroduced recently [2]. This ratio was shown to overestimate compliance [5] and should only be used for comparison.
- The *area method*, where the area under the diastolic aortic pressure divided by the pressure difference between start and endpoint is set equal to decay time.

$$RC = \int_{t_1}^{t_2} \frac{P}{P_1 - P_2} dt$$

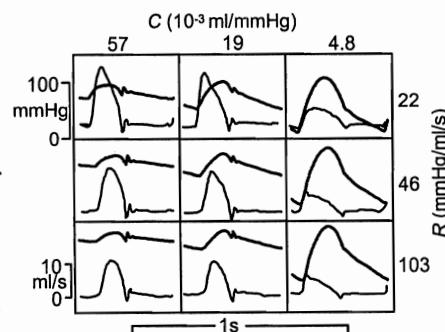
Knowing the RC time and calculating  $R$  by the ratio of mean pressure and mean flow the compliance can be derived [3,4].

- The *two-area method* is based on the following equation:

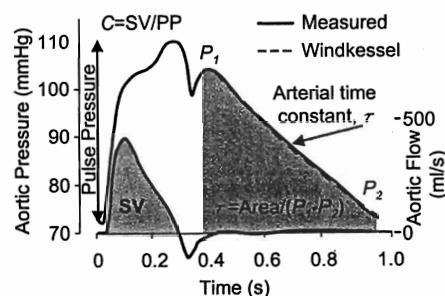
$$\int_{t_1}^{t_2} Q dt = C \cdot (P_2 - P_1) + \frac{1}{R} \int_{t_1}^{t_2} P dt$$

The equation is applied to two periods of the cardiac cycle; the period of onset of systole to peak systole and the period from peak systole to the end of diastole. Thus two equations with two unknowns,  $R$  and  $C$ , are obtained [7].

- The *pulse pressure method* is based on fitting the systolic and diastolic pressures predicted by the two-element Windkessel with measured aortic flow as input, to the measured values of systolic and diastolic pressure. Although the two-element Windkessel does not produce correct wave shapes the low frequency impedance is very close to the actual impedance and systolic and diastolic pressure are mainly determined by low frequencies [10].
- The *parameter estimation method* fits the three-element or four-element Windkessel using pressure



**AORTIC PRESSURE AND FLOW** resulting from an isolated cat heart pumping into a three-element windkessel. The effect of changes in peripheral resistance (increasing downwards) and arterial compliance (decreasing to the right) are shown. The control condition (cat, left top panel). The advantage of the use of such a model is that all venous and cardiac parameters can be kept constant while varying one; here resistance or compliance. Adapted from [1] used by permission.



**TOTAL ARTERIAL COMPLIANCE DETERMINATION.**

- Stroke volume divided by Pulse Pressure.
- The decay time,  $\tau$ , of diastolic aortic pressure,  $\tau = RC$ . With  $R = P_{mean}/Q_{mean}$ ,  $C$  can be derived.
- Area method. The area under the diastolic aortic pressure divided by the pressure difference is used as a measure of the decay time.

and flow as a function of time. When aortic flow is fed into the Windkessel the pressure is predicted. This pressure can be compared to the measured pressure. By minimization of the summed Root Mean Square Errors, RMSE, of the difference between measured and predicted pressures the best Windkessel parameters are obtained. In this way all the Windkessel parameters can be derived including a good estimate of characteristic impedance. Using the three-element Windkessel compliance is overestimated [5], but this is not the case using the four-element Windkessel [8]. Also pressure may be used and optimization of flow is then performed [9].

- The *input impedance method* fits the input impedance of the three-element of four-element Windkessel model to the measured input impedance, in a way similar to method 5.
- The *transient method* can be applied when pressure and flow are not in the steady state. Peripheral resistance can then not be calculated from mean pressure and mean flow, because aortic flow is not equal to peripheral flow. Using the three-element Windkessel with flow as input, pressure may be calculated while storage of blood in the large conduit arteries is accounted for. By curve fitting of the Windkessel parameters to obtain minimal difference between measured and predicted pressure the Windkessel parameters can be estimated accurately [11].
- The *wave velocity method*. Another method, not based on the Windkessel but on transmission of waves is mentioned here too. Using the Moens-Korteweg equation wave speed (in practice the foot-to-foot wave velocity,  $c_{ff}$ ) can be related to compliance  $c_{ff} = \sqrt{V\Delta P/\Delta V\rho}$  (see Chapter 20). When the wave speed between carotid and iliac arteries is measured, length  $l$ , and average cross-sectional area of the aorta is also determined,  $V$  can be calculated and total aortic compliance is obtained. Since the ascending aorta and other arteries are not included, total aortic compliance is lower than total arterial compliance.

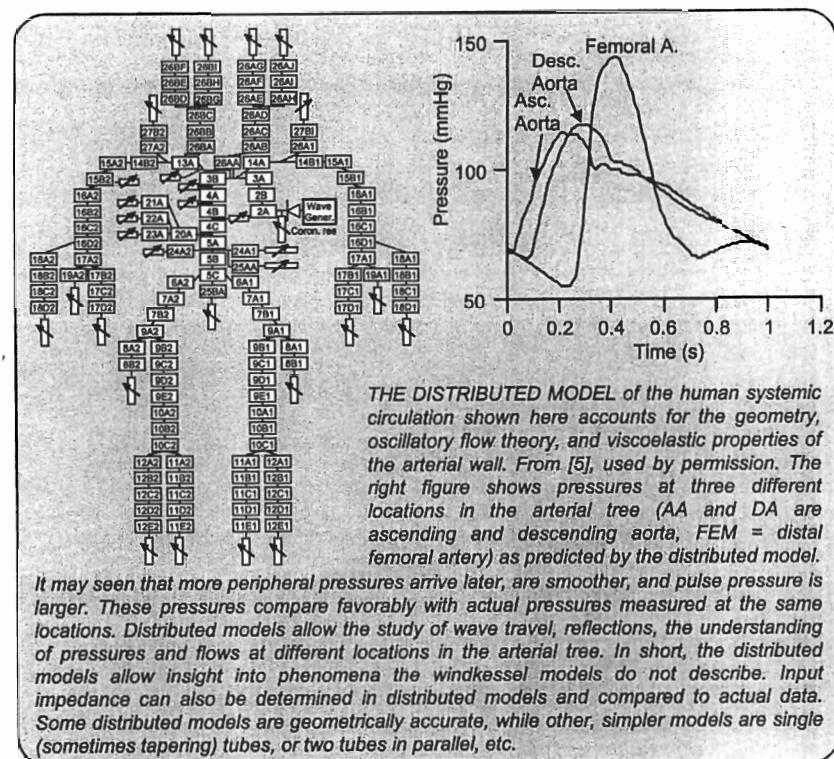
It should be emphasized that all Windkessel-based methods are based on accurate pressure measurement in the proximal aorta. Methods 1 - 3 only require measurement of Cardiac Output, while methods 3 - 8 require ascending aortic flow wave shape. Method 9 requires two accurate pressure measurements.

Finally the three- or four-element Windkessel models can be used in lumped models of the whole cardiovascular system in combination with lumped cardiac models (See [6] as an example).

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### Description

The Windkessel models give an overall, lumped description of the arterial tree. Thus Windkessel models do not permit the study how pressure and flow waves propagate in the arterial tree. Modeling wave propagation requires the use of distributed models, such as the one shown in the box figure. The basic idea of distributed models is to break up the arterial tree into small segments, whose geometry and mechanical properties are known. The wave transmission characteristics of each arterial segment can be described using Womersley's oscillatory flow theory (Chapter 8) or electrical transmission line theory (Appendix 3).

Distributed models of the arterial tree can also be constructed based on the one-dimensional (simplified) form of the blood flow equations describing the conservation of mass and momentum:

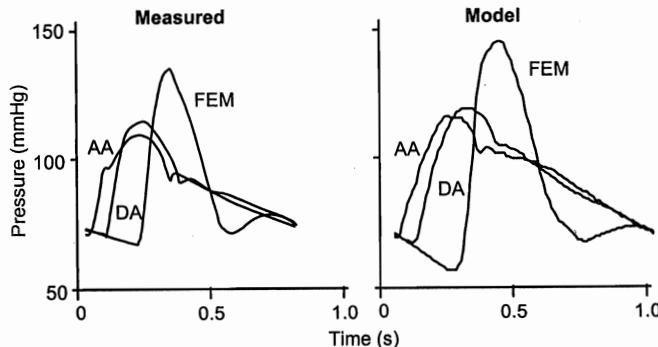
$$\partial Q / \partial x + \partial A / \partial t = 0$$

$$\partial Q / \partial t + \partial(Q^2 / A) / \partial x = -(1 / \rho) \cdot A \cdot \partial P / \partial x - 2\pi r \cdot \tau / \rho$$

## Arterial Hemodynamics

where  $A$  is the vessel cross-sectional area and  $\tau$  is wall shear stress, usually estimated using Poiseuille's law. The two equations above have 3 variables: pressure  $P$ , flow  $Q$ , and area  $A$ . Therefore a constitutive law relating cross-sectional area,  $A$ , to pressure,  $P$ , is needed to form a system of 3 equations with 3 unknowns, which can be easily solved using different numerical techniques (i.e., finite differences, or method of characteristics).

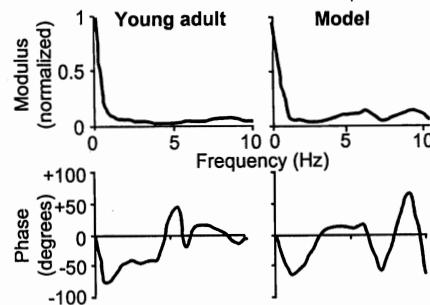
Distributed models have been extensively used to study different aspects



CENTRAL AND PERIPHERAL PRESSURE WAVES of a distributed model, compared with actual pressure waves measured in similar locations in the human. AA = Ascending Aorta, DA = Descending Aorta, and FEM = Femoral Artery.

of pressure and flow propagation, such as the effects of viscoelasticity, the effects of different forms of arterial disease on pressure and flow waves, wave reflections, the relation of peripheral to central pressure waves, etc. [3,4,5]. Distributed models predict pressure and flow waves that are fairly accurate and compare well to actual waves measured in the human. This can be seen in the figure, where measured arterial pressure waves in the human are compared to predicted pressure waves of a standard distributed model. Beyond an apparently good qualitative agreement, well known aspects of pressure wave propagation in arteries, such as the systolic pressure amplification, the smoothening of the pulse and the appearance of a secondary reflection in the diastolic part of a pressure wave in a peripheral artery are well predicted.

Global aspects of the distributed models, such as the aortic impedance, (figure at right) also compare favorably to reality. The figure shows the modulus and phase of the input impedance derived from a distributed human systemic arterial model as well as the input impedance measured in a



INPUT IMPEDANCE of a distributed model (left), compared with the input impedance measured in a young healthy adult (right). The impedance modulus is normalized to the peripheral resistance to facilitate the comparison.

## Distributed Models

young healthy adult. The figure also shows that the distributed model predicts all the typical features of the arterial input impedance. The rapid drop in modulus for the first few harmonics, the relatively flat modulus in the medium frequency range, and the correspondence between the point of minimum in impedance modulus and the zero-crossing of the phase angle.

## Single tube and T-tube models

Windkessel models and distributed models of the arterial tree represent the two extremes of available models of the arterial tree: the former are simple, contain 3 - 5 global parameters and therefore are easy to use but lack all aspects of wave travel. The latter offer a fairly complete representation of the arterial tree in terms of hemodynamics but require a large number of parameters namely geometry and elasticity of all arterial segments, and therefore are rather cumbersome in their use. Given the above limitations, several researchers have proposed models that are relatively simple but allow for the phenomena of wave travel and reflections. The simplest are the single tube and the asymmetric T-tube models. The single tube models are, as the name suggests, the combination of a tube representing mainly the aorta connected to a peripheral resistor or Windkessel as a model of the peripheral beds. The simplicity of the model is also its main handicap in the sense that all distal reflections come from a single point. A slightly more realistic model is a single tube with geometric tapering as model of the aorta. Asymmetric T-tube models, on the other hand, appear to yield a better description of the arterial tree in terms of input impedance and wave reflections. The asymmetric T-tube model consists of two parallel tubes, a short and small one representing the arterial tree of the upper extremities (head and arms) and a larger size tube accounting the thoracic and abdominal aorta and their branches including the legs [1,2]. The two tubes terminate either with a resistance or a Windkessel as model of the corresponding terminal bed.

## Physiological and clinical relevance

Distributed models have been used mostly for research as analytical tools because they are realistic for simulating a variety of physiological and pathological situations. Although, in principle, distributed models can be used to derive useful parameters of the arterial tree based on *in vivo* measurements, clinical use is difficult because of the large number of parameters required to construct a 'per patient' model.

In arterial modeling research the choice of model should depend on the degree of detail required and the focus desired. To understand the effect of total arterial compliance on integrated quantities such as aortic pressure and Cardiac Output, the Windkessel models suffice. To model detailed effects, such as local flows and pressures and their transmission, one needs to use distributed models.

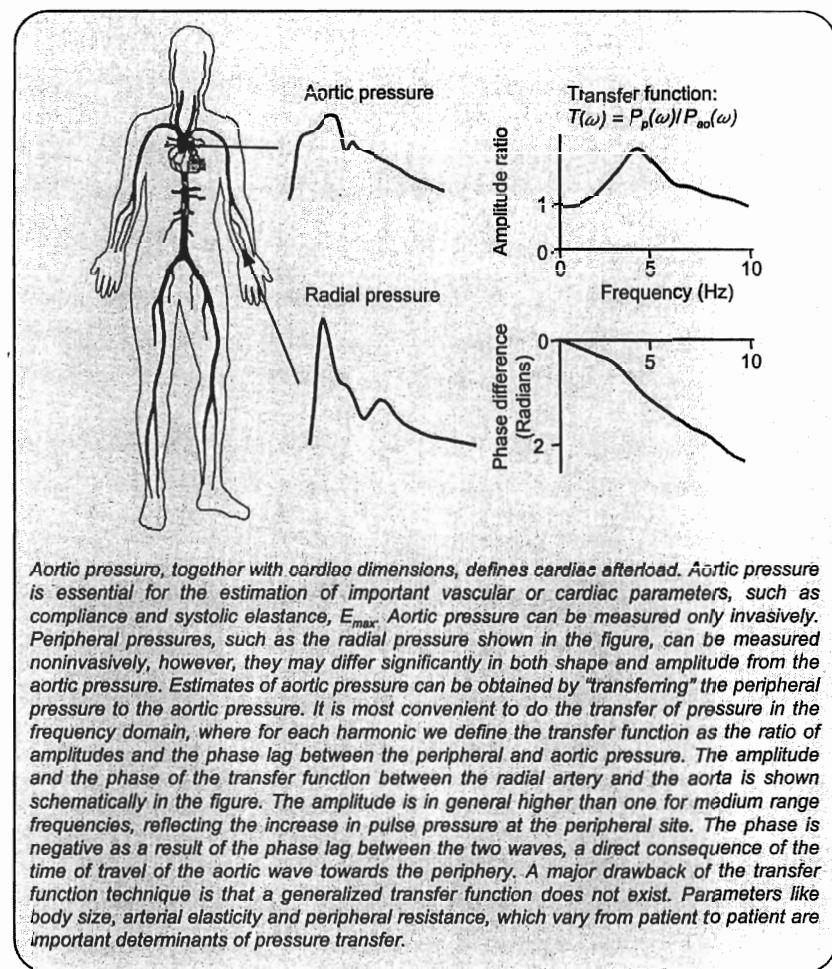
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## Chapter 26

## TRANSFER OF PRESSURE



*Aortic pressure, together with cardiac dimensions, defines cardiac afterload. Aortic pressure is essential for the estimation of important vascular or cardiac parameters, such as compliance and systolic elastance,  $E_{max}$ . Aortic pressure can be measured only invasively. Peripheral pressures, such as the radial pressure shown in the figure, can be measured noninvasively, however, they may differ significantly in both shape and amplitude from the aortic pressure. Estimates of aortic pressure can be obtained by "transferring" the peripheral pressure to the aortic pressure. It is most convenient to do the transfer of pressure in the frequency domain, where for each harmonic we define the transfer function as the ratio of amplitudes and the phase lag between the peripheral and aortic pressure. The amplitude and the phase of the transfer function between the radial artery and the aorta is shown schematically in the figure. The amplitude is in general higher than one for medium range frequencies, reflecting the increase in pulse pressure at the peripheral site. The phase is negative as a result of the phase lag between the two waves, a direct consequence of the time of travel of the aortic wave towards the periphery. A major drawback of the transfer function technique is that a generalized transfer function does not exist. Parameters like body size, arterial elasticity and peripheral resistance, which vary from patient to patient are important determinants of pressure transfer.*

### Description

Peripheral pressures can be measured noninvasively by different techniques. For example, finger pressure can be reliably measured by photoplethysmography, and radial artery and carotid artery pressure waveforms can be obtained with applanation tonometry. Both techniques are commercially available. Most clinicians use peripheral pressures and typically brachial pressure obtained with the classical sphygmomanometer. Brachial pressure is then used as a substitute for aortic pressure, or, even more so, as a global arterial pressure indicator. However, peripheral and central aortic pressures are not the same. The pressure waveform and the systolic and diastolic pressures can be substantially different between locations (see figure in the

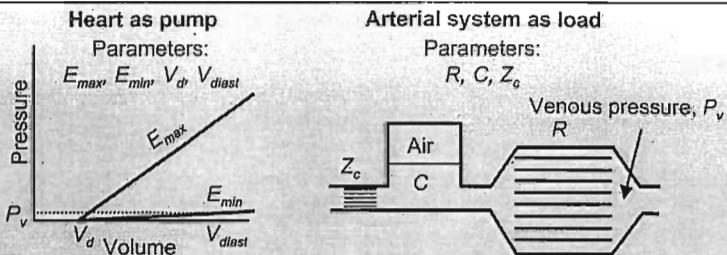


Table: Percent changes in pressure and stroke volume, SV, resulting from doubling a single cardiac or arterial parameter.

	$P_{sys}$	$P_{dias}$	SV
$Z_c$	+9	0	0
$R$	+41	+90	-28
$C$	-10	+22	+5
$T$	-50	-90	+28
$E_{max}$	+40	+32	+33
$E_{min}$	-100	-100	-100
$P_v$	+100	+100	+100

Thus a 20% change in heart rate results in a 10% change in systolic pressure and an 18% in diastolic pressure. The minus sign indicates a decrease with an increase in a parameter.

period,  $T$ . The  $E(t)$  curve, when normalized to peak,  $E_{max}$ , and time to peak,  $T_p$ ,  $E_N(t/T_p)$ , is constant in shape, and can be used as an independent variable. The three elements of the windkessel are peripheral resistance,  $R$ , arterial compliance,  $C$ , and aortic characteristic impedance,  $Z_c$ . The quantitative contribution of the heart and arterial system to pressure and flow is given in the table. Dimensional analysis showed that  $RC/T$  and  $CE_{max}$  are parameters that couple the heart and load, and they play an important role in pressure and stroke volume. Since the normalized  $E(t)$  curve, describing the heart, and the normalized input impedance, describing the arterial system, are similar in different mammals the wave shapes of pressure and flow are similar in mammals as well.

AORTIC PRESSURE AND FLOW RESULT from the interaction of the heart, the pump, and the arterial system, the load. The quantitative contribution of the heart and the arterial system to pressure and flow is important in the understanding of hypertension, cardiac failure and other cardiovascular diseases. In the figure we show the parameters that describe the heart on the basis of the pressure-volume relation, left, and those that describe the arterial load, on the basis of the arterial windkessel, right. Using this limited number of parameters their quantitative contribution to systolic and diastolic pressure and stroke volume can be worked out. The cardiac parameters are venous filling pressure,  $P_v$ , and the slopes of the diastolic and systolic pressure-volume relations,  $E_{min}$  and  $E_{max}$ , the intercept of the pressure-volume relation  $V_d$ , and the heart

## Description

Blood pressure and Cardiac Output result from the interaction of the heart and arterial load. The contribution of the heart is obvious, because without its pumping action pressure and flow would not exist. However, the quantitative contribution of the heart and arterial load to pressure and flow under different physiological conditions and during various diseased states has not been sufficiently recognized. To quantitatively analyze the cardiac and arterial contributions to systolic and diastolic pressure and Stroke Volume, we make use of the simplified descriptions of the cardiac pump and the arterial system. The heart is described by the varying elastance model (Chapter 13), and the arterial system is described by the three-element Windkessel model (Chapter

24). Using these models the contribution of each parameter to pressure and flow can be quantified.

### *Dimensional analysis*

Dimensional analysis, or the concept of similitude, is a powerful method to systematically derive relations of a system and offers two major advantages [3]. First, it reduces the number of variables, and second, it groups the cardiac and arterial parameters in dimensionless terms, which are automatically scaled to heart rate and body size. This will be a particularly important issue when we discuss comparative physiology (Chapter 30). The parameters that describe the heart as a pump, including venous filling pressure, and the arterial system as the load are given in the box. The total number of parameters is 8: 5 for the heart and 3 for the arterial system.

The dependent variables systolic and diastolic pressure ( $P_s$  and  $P_d$ ) and Stroke Volume,  $SV$ , can be written as a function of these eight cardiac and arterial parameters. Dimensional analysis implies that when the variables and the parameters are non-dimensionalized, the number of non-dimensional parameters can be reduced by three. Three is the number of reference dimensions (time, force and length), describing the variables [3]. Thus five non-dimensional parameters remain. An intelligent choice is the following [6]:

$$P_s/P_v = \Phi_1 (Z_c/R, RC/T, CE_{min}, E_{max}/E_{min}, E_{min}V_d/P_v)$$

$$P_d/P_v = \Phi_2 (Z_c/R, RC/T, CE_{min}, E_{max}/E_{min}, E_{min}V_d/P_v)$$

$$SV \cdot E_{min}/P_v = \Phi_3 (Z_c/R, RC/T, CE_{min}, E_{max}/E_{min}, E_{min}V_d/P_v)$$

The symbols are explained in the box. The next step is to find the dependence of the non-dimensional variables on the non-dimensional parameters. It turns out experimentally that the parameter  $E_{min} \cdot V_d/P_v$  does not contribute to  $P_s/P_v$  and  $P_d/P_v$ ; that  $Z_c/R$  does not determine  $P_d/P_v$  and  $SV/V_d$ ; while  $E_{max}/E_{min}$  does not determine  $SV \cdot E_{min}/P_v$ . The contribution of  $Z_c/R$  to  $P_s/P_v$  turns out to be small [6] and is neglected. The relations then can be simplified to:

$$P_s/P_v \approx \Phi_1 (RC/T, CE_{min}, E_{max}/E_{min})$$

$$P_d/P_v \approx \Phi_2 (RC/T, CE_{min}, E_{max}/E_{min})$$

$$SV \cdot E_{min}/P_v \approx \Phi_3 (RC/T, CE_{min}, E_{min} \cdot V_d/P_v)$$

In all non-dimensional variables we see that the parameters  $RC/T$ , and  $CE_{min}$  appear. We call them ventriculo-arterial coupling parameters. This emphasizes the fact that the interaction of pump and load determines pressure and flow.

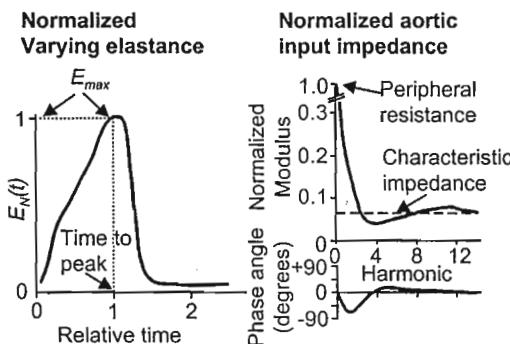
The Frank-Starling mechanism also emerges clearly from the above equations. Leaving all parameters the same, the pressures are simply proportional to venous pressure,  $P_v$ ,  $SV$  is also related to filling pressure, but in a more complex way.

The pressures also are dependent on  $E_{max}/E_{min}$  a measure of contractility of the heart. The Stroke Volume is also described by the rather complex term

$E_{min} \cdot V_d / P_v$ , which is related to diastolic ventricular filling and can be written as  $V_d / (V_{diast} - V_d)$ , with  $V_{diast}$  end-diastolic ventricular volume.

On the basis of the results obtained with the dimensional analysis we can perform a sensitivity analysis of pressure and Stroke Volume to individual parameters. The results are given in the table in the box.

We note that the normalized parameters  $RC/T$ ,  $CE_{min}$ ,  $E_{max}/E_{min}$  do not depend on body size, so that for similar venous pressures, aortic systolic and diastolic pressures will be similar in all mammals (see Chapter 30). Stroke Volume does depend on body size. The wave shapes of aortic pressure and flow result from the shape of the  $E(t)$  curve describing the pump and the input impedance describing the arterial load. Both, when normalized, are body size independent [5,7], explaining why aortic pressure and flow look alike in all mammals (Chapter 30).



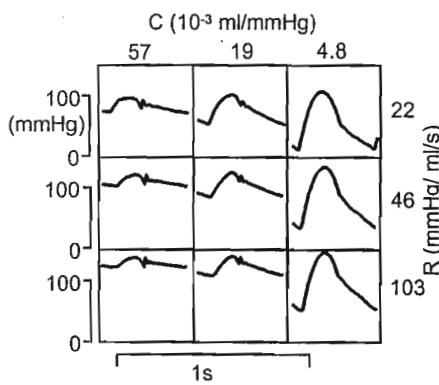
The normalized elastance curve and the normalized input impedance curve are similar, resulting in similar wave shapes of aortic pressure and flow.

## Physiological and clinical relevance

The analysis shows in quantitative terms the contribution of cardiac and arterial parameters to blood pressure and Stroke Volume. It may be seen from the table in the box that resistance has a much stronger effect on systolic blood pressure than compliance has. However, changes in compliance are often considerably larger than resistance changes. For instance, between the ages of 20 and 70 years compliance may decrease by a factor of 3, thus increasing systolic blood pressure by 15%, while the age related resistance increase is about 10% resulting in a systolic pressure increase of slightly over 4%.

On the basis of the dimensionless parameters shown above it may be suggested to use  $E_{max} / E_{min}$  as a measure of contractility, because this ratio is size independent. The  $E_{max}$  alone is, of course depending on the ventricular volume.

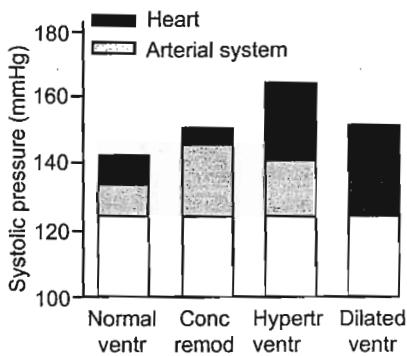
The theoretical results can be compared with biological data. Experimental data [1] obtained from the isolated heart loaded with a



AORTIC PRESSURE resulting from an isolated cat heart pumping into a three-element windkessel. The effect of changes in peripheral resistance and total arterial compliance are shown. Note that systolic pressure is little affected by decreasing compliance. Adapted from [1], used by permission.

Windkessel model indeed show that compliance changes alone have a small effect on systolic blood pressure and a larger effect on diastolic blood pressure. When compliance is decreased *in vivo* other parameters also change and systolic pressure increases and diastolic pressure decreases [2]. The main difference between the *ex vivo* and *in vivo* results is the adaptation of the heart during the decrease in compliance. The *ex vivo* heart, including filling, was unchanged while *in vivo* the heart adapts and Cardiac Output diminishes less than in the *ex vivo* situation. Thus, the changed cardiac function *in vivo* has an effect on blood pressure.

In the literature it is well established that hypertension results in ventricular hypertrophy and therefore a higher  $E_{max}$ . However, it is often not realized that hypertrophy causes changes in the properties of the cardiac pump such as increased wall thickness and that these changes may, in turn,



**CARDIAC AND ARTERIAL CONTRIBUTIONS TO SYSTOLIC pressure increase in four groups of hypertensive patients.** Several stages in cardiac changes are depicted, 1. Normal ventricle; 2. Concentric remodeling; and 3. Hypertrophied ventricle; and 4. Dilated left ventricle. Cardiac and arterial parameters derived from [5]. The white bar gives the systolic pressure of the normal cardiovascular system. In concentric remodeling most of the pressure increase results from the change in the arterial system. When the ventricle is dilated in hypertension most of the pressure increase is caused by the heart. Adapted from [4], used by permission.

contribute to a further increase in blood pressure.

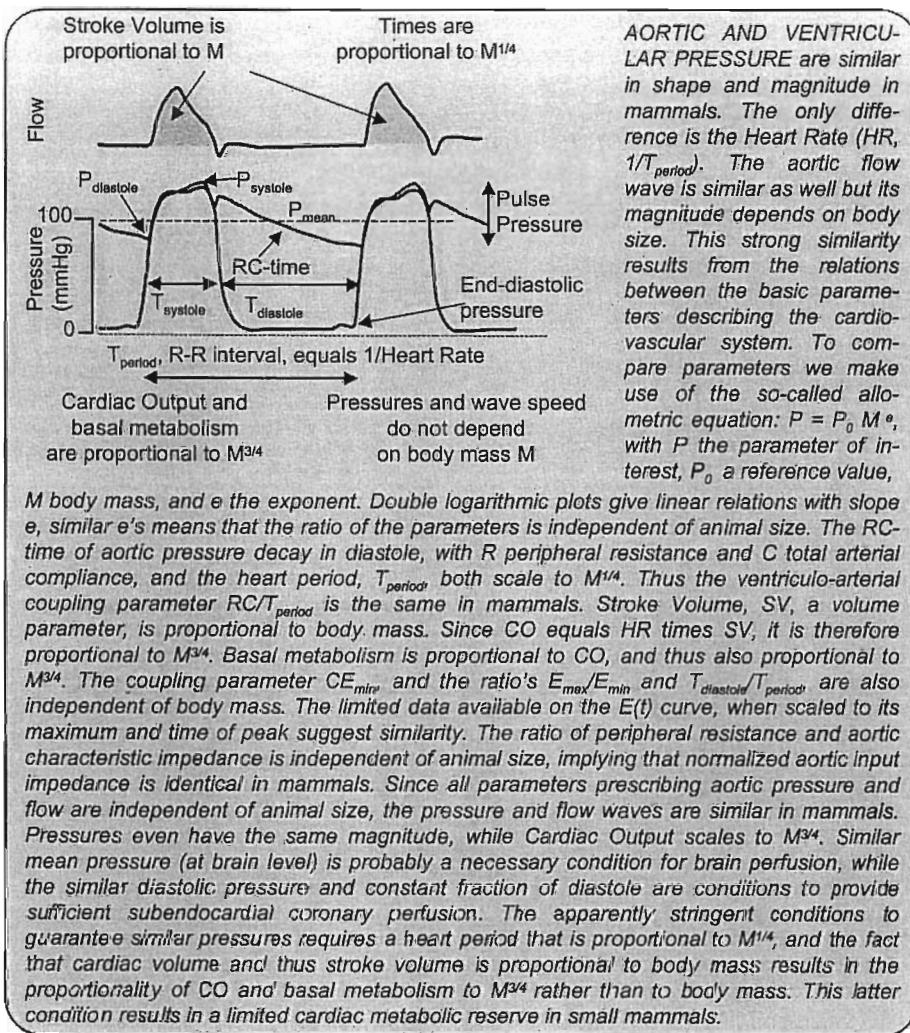
#### Contribution of arterial system and heart in systolic hypertension

Using the models as given in the figures in the box, the contributions of the heart and arterial system in four groups of hypertensive patients were calculated [4]. It may be seen that in concentric remodeling the increase in systolic blood pressure is mainly the result of the altered arterial system, while in eccentric hypertrophy the contribution to the increased systolic pressure is mainly the result of changed cardiac properties. This example therefore shows that both heart and arterial system need to be considered in hypertension research.

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7. Westerhof N, Elzinga G. Normalized input impedance and arterial decay time over heart period are independent of animal size. *Am J Physiol* 1991;261:R126-R133.



## Description

Comparative physiology is based on the allometric equation:

$$PA = PA_0 \cdot M^e$$

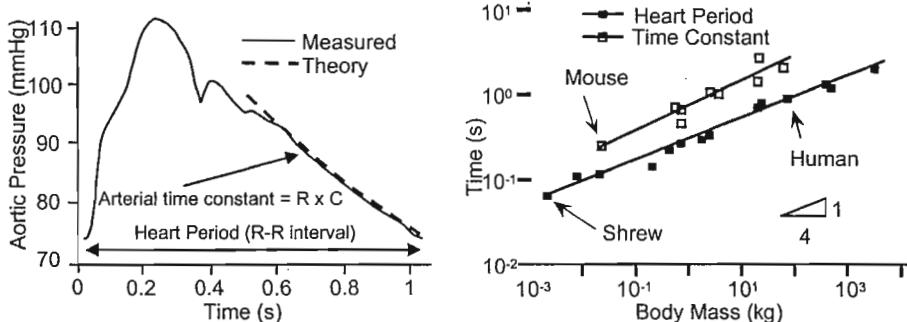
with  $PA$  the parameter of interest,  $PA_0$  a reference value,  $M$  body mass, and  $e$  the exponent. When the logarithm of both sides is taken the equation can be rewritten as:

$$\log PA = \log PA_0 + e \log M$$

This equation states that, when a parameter  $PA$  is plotted against body mass  $M$ , in a double logarithmic plot, a straight line with slope  $e$  is obtained. If two parameters have the same slope (same  $e$ ), the ratio of the parameters

does not depend on body mass, i.e., the ratio is independent of the size (mass) of the animal.

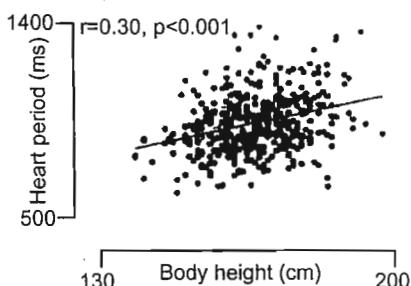
The coupling parameter  $RC/T$  (see Chapter 29) is an example of the study of comparative physiology, where it is shown that the characteristic time of the arterial system, RC-time, and the characteristic time of the heart, the heart period,  $T$ , have the same exponent implying that their ratio is independent of body mass [12]. The similar pulse pressure found in mammals can be understood on the basis of this mass-independence as follows. Total arterial compliance,  $C$ , is proportional to Stroke Volume divided by pulse pressure,  $PP$  so that  $C \propto SV/PP$ . Mean pressure is equal to Resistance,  $R$ , times Cardiac Output:  $P_{mean} = R \cdot CO$ . The Cardiac Output equals Heart Rate times Stroke Volume, and Heart Rate =  $1/T$ . Therefore  $P_{mean}/PP \propto RC\text{-time}/T$ . This implies that, with similar mean pressure, the pulse pressure, and therefore also the systolic and the diastolic pressures are the same in mammals. The



AORTIC PRESSURE (left) AND A LOG-LOG PLOT OF HEART PERIOD AND RC-TIME (right). The aortic pressure shows an exponential decay in diastole, characterized by the arterial parameter RC-time, i.e., peripheral resistance,  $R$ , times total arterial compliance,  $C$ . The heart period is a cardiac parameter. Both times show an increase with body mass with an exponent of  $\frac{1}{4}$ . This implies that the ratio of the two, the ventriculo-arterial coupling parameter  $RC/T_{period}$  is the same in mammals. Adapted from [12], used by permission.

ratio of Pulse Pressure and mean pressure,  $PP/P_{mean}$ , is called the fractional pulse pressure.

The finding that the heart period increases with body mass predicts, even in a single species that heart period increases also with body length. This was indeed shown to be the case in man.



HEART PERIOD RELATES TO BODY HEIGHT in humans. Body height is a measure of body mass. Adapted from [10], used by permission.

In general, volumes are proportional to body mass, i.e.,  $M^{+1}$  and so are cardiac volume and Stroke Volume [5]. With  $CO = HR \cdot SV$ , it follows that  $CO$  is proportional to  $M^{3/4}$ . This is indeed what is found and is shown in the first figure on the next page.

Other comparative data are scarce but if we assume similar material properties, and with volumes proportional to body mass [1, 5], it follows that the slope of the diastolic and systolic pressure-volume relations, are proportional to  $M^{-1}$ , and also that

total arterial compliance,  $C$ , is proportional to body mass. Thus, the coupling parameters  $CE_{min}$  and  $CE_{max}$ , are independent of body mass (see Chapter 29). The ratio of  $E_{max}$  and  $E_{min}$  equals systolic over diastolic pressure for isovolumic beats and this ratio is similar in mammals, thus  $E_{max}/E_{min}$  is size independent.

In the data published on the  $E(t)$  curve, those of man and dog are not dissimilar in shape, when normalized with respect to time of peak and peak value [9]. Quantitative data on a whole range of mammals is not available yet.

When we plot the characteristic impedance and peripheral resistance as a function of body mass we find parallel lines again

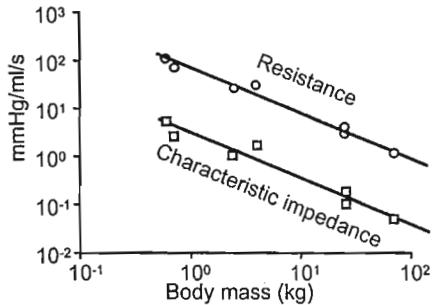
**CARDIAC OUTPUT AND BASAL METABOLISM** are proportional and increase with body mass to the power  $\frac{3}{4}$ . Data on metabolic rate from [8] and data on CO from [1], used by permission.

(figure below left). This implies that this ratio is similar in mammals. Therefore the aortic input impedance is similar when scaled with respect to the characteristic impedance or peripheral resistance and plotted as a function of harmonic, i.e., as multiples of the heart rate (Appendix 31). When a three-element Windkessel is assumed as acceptable model of the systemic arterial tree (Chapter 24), the input impedance can be written as:

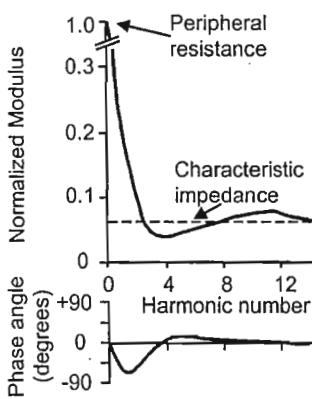
$$Z_{in} / Z_c = \frac{1 + R/Z_c + 2 \cdot \omega \cdot n \cdot RC/T}{1 + 2j \cdot \omega \cdot n \cdot RC/T}$$

where  $n$  the harmonic number. With  $RC/T$  and  $R/Z_c$  independent of animal size, the normalized arterial input impedance is the same as shown in the figure below right [12]. Thus, the aortic pressure and flow wave shapes are related in a similar way in all mammals.

This in turn implies that with similar pressure wave shapes, the flow waves are similar too.

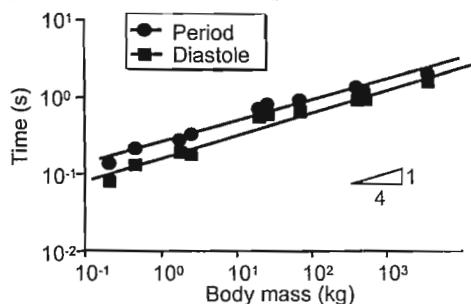


**THE RATIO OF PERIPHERAL RESISTANCE** and aortic characteristic impedance is independent of animal size. Adapted from [12], used by permission.



**NORMALIZED INPUT IMPEDANCE** is similar in mammals. This implies that the harmonics of pressure and flow are treated similarly and thus their wave shapes are the same.

The non-dimensional ventriculo-arterial coupling parameters,  $CE_{max}$  and  $RC/T$  (Decay time of diastolic aortic pressure over heart period, Chapter 29) are independent of animal size. Together with the above the final result is that in all mammals pressure waves are similar in shape and magnitude and flow waves are also similar in shape, but the magnitude relates to body mass to the power  $3/4$ . It was also shown that the size of the heart results in optimal external power production [4].



HEART PERIOD AND DURATION OF DIASTOLE are plotted as a function of body mass. The parallel lines imply that diastole is a fixed fraction of the heart period. Adapted from [12], used by permission

It has also been suggested that shear stress would be similar in mammals too (Chapters 27 and 28). Shear stress is proportional to  $Q/r^3$ , and since  $CO$  scales to  $M^{3/4}$ , and  $r$  to  $M^{1/3}$ , shear stress scales to  $M^{3/4}/M = M^{-1/4}$ . Shear stress is probably not very tightly controlled (Chapters 27 & 28) and certainly is not the same in different vessels.

The allometric relations of heart period and duration of diastole are given here. The relations are again parallel, which means that in mammals diastole is a constant fraction of the heart period.

Subendocardial perfusion mainly takes place in diastole, and thus depends on diastolic pressure duration of diastole. With these two quantities similar, the coronary fractional perfusion time (Chapter 18) is similar in mammals as well, so that coronary perfusion conditions are also similar.

#### Basal whole body and cardiac metabolism

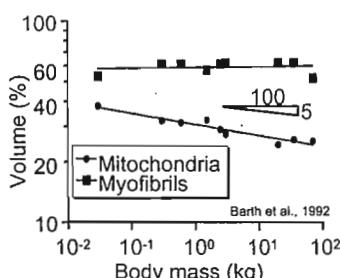
Basal whole body metabolism and Cardiac Output are both proportional to body mass as  $M^{3/4}$  (figure on the previous page). Why  $CO$  is proportional to  $M^{3/4}$  was explained above. Apparently metabolism is related to  $CO$ , but other suggestions have been given [11]. Basal metabolism and  $CO$  may be closely related because oxygen carrying capacity of the blood is similar in mammals.

In summary, the rigorous control of blood pressure appears to demand that heart rate is coupled to the  $RC$ -time of the arterial system. This, in combination with a  $SV$  that is proportional to body mass, results in the  $3/4$  power law of  $CO$  and whole body metabolism.

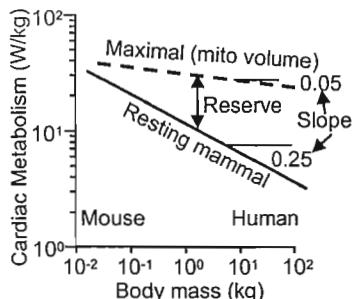
#### Cardiac metabolism

It is well known that cardiac metabolism per gram heart tissue is higher in small than in large animals. The oxygen consumption is proportional to the Pressure Volume Area, PVA, times Heart Rate, HR, or approximately  $[P_{systolic} \cdot SV \cdot HR + \frac{1}{2} P_{systolic} \cdot (V_{end-systolic} - V_d)] \cdot HR$  (see Chapter 15), and, since volumes scale to  $M^1$ ,  $VO_2$  relates to body mass to the power  $3/4$  as well. This  $3/4$  law of total heart metabolism implies that when cardiac metabolism is expressed per gram tissue it decreases with increased body mass to the power  $\frac{1}{4}$ , i.e.,  $M^{-1/4}$ . Mitochondrial relative volume, as a measure of maximal energy

expenditure per unit mass, decreases with body mass as  $M^{-0.05}$  [2]. In other words, the difference between maximal metabolism and resting metabolism, i.e. the metabolic reserve, decreases in smaller mammals.



THE FRACTIONAL VOLUMES of myofibrils and mitochondria in cardiac muscle cells as a function of body mass. Mitochondrial volume is a measure of maximal energy production and use. Data from [2].



MAXIMAL AND RESTING energy expenditure per gram both decrease with animal size. Since the slopes are different the energy reserve for small mammals is small.

### Pulse wave velocity and reflections

Experimental data show that pulse wave velocity is independent of animal size. This can be seen from basic vascular data where the Young modulus of elasticity,  $E$ , and wall thickness over radius,  $h/r$ , are species independent and, as a consequence wave speed (Moens-Korteweg equation),

$$c = \sqrt{\frac{h \cdot E}{2 \cdot r \cdot \rho}}$$

is independent of body size as well.

The return of the reflected waves at the heart equals traveled length over wave speed. Length of the arteries is proportional to  $M^{1/3}$ , so that the return time of reflections is also proportional to  $M^{1/3}$ . The heart period is proportional to  $M^{1/4}$ . This small difference in power makes reflections return in the about the same part of the cardiac cycle in most mammals.

### Physiological and clinical relevance

Comparative physiology of the cardiovascular system shows that the heart and arterial system act to produce similar magnitude and wave shape of pressures and similar wave shapes of flow in mammals. This strongly suggests that pressure magnitude and wave shape are important. It has indeed been shown that high pressure, e.g., hypertension, is a strong indicator of cardiovascular pathology. Recent epidemiological data point to the strong relation between pulse pressure and cardiovascular morbidity and mortality [3,7]. The magnitude of pulse pressure, together with the about  $2.5 \cdot 10^9$  pulsations in a lifetime, may play a role in fatigue and fracture of the arterial wall. Martyn and Greenwald [6] argue that the synthesis of elastin is slow and that damage takes years to repair. The decrease in elastin may be the

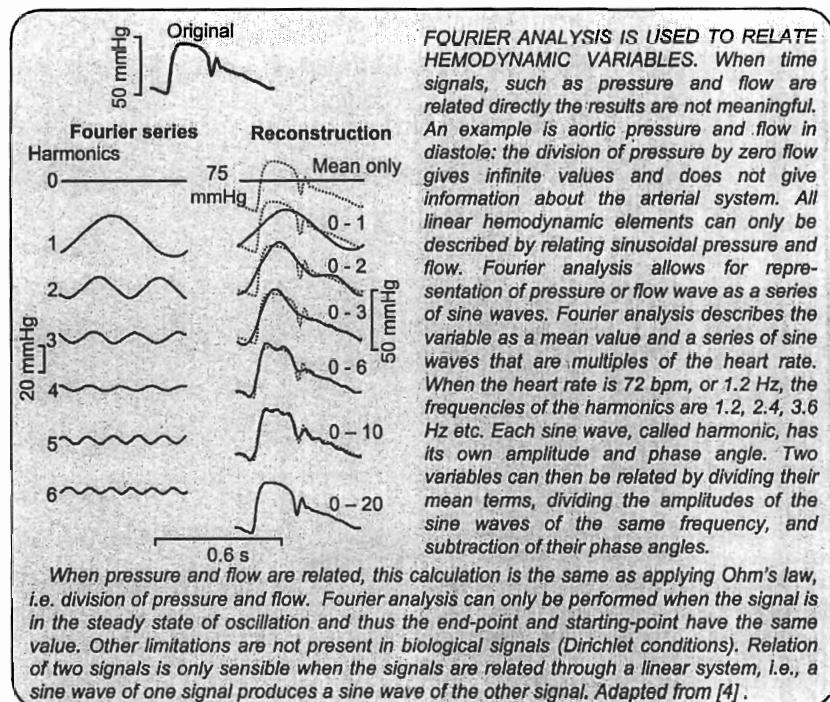
reason that with age aortic diameter increases and the wall becomes stiffer, because vessel elasticity becomes gradually more determined by the collagen, which gradually replaces elastin.

It has been argued that all mammals have the same number of heartbeats over their life span. Thus small animals with high heart rates live shorter than large animals. Vascular damage may be an argument. However, metabolism per gram decreases with increasing body mass. The lower metabolism per gram in larger mammals may imply a lower production of oxygen radicals and less cellular damage.

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## Appendix 1 TIMES & SINES: FOURIER ANALYSIS



### Description

Fourier analysis breaks a periodic signal up in a series of sine waves. The sine waves of two hemodynamic variables (e.g., pressure and flow) can then be used to derive an input-output relation, such as an input impedance (Chapter 23) or transfer function (Chapter 26). The technique to perform Fourier analysis is now readily available and therefore easy to perform. It is not a curve fitting technique but a straightforward calculation. The analysis results in a mean term and series of sine waves. The mean term is often called the zeroth harmonic. The sine waves have frequencies that are multiples of the basic frequency, e.g., heart rate, and are called harmonics. The first harmonic equals the frequency of the heart rate, the second harmonic is twice the heart rate, etc.

In the left part of the figure in the box the individual harmonics are given each having an amplitude and phase angle. The phase angle is best seen from the starting point of the sine wave. We see that the amplitudes of the harmonics are decreasing in amplitude. On the right hand side the reconstruction is presented. It is simply the addition of the sine waves at the same moments in time. Using 10 harmonics the signal is almost completely reconstructed, and with 20 harmonics the signal is completely reconstructed. This means that aortic pressure is described by approximately 15 harmonics. It turns out that the smoother the signal the fewer harmonics are required to

describe it. Ventricular pressure can be described by about 10 harmonics. Thus, in general, the information in hemodynamic signals such as pressure, flow and diameter contains information up to 15 harmonics, i.e., 15 times the heart rate.

This knowledge is important with respect to measurement techniques. To measure a sine wave well at least two points are required (the Nyquist criterion [1]). Thus sampling should be done with at least twice the highest frequency, i.e. the highest harmonic, in the signal. In hemodynamics this means that the sampling rate should be at least twice as high as the frequency of the highest harmonic, thus 30 times the heart rate. If dealing with human hemodynamics, with a heart rate of 60 bpm, the rate is 1 cycle per second 1 (1 Hz) and sampling should be done with a rate higher than 30 samples per second. If we measure in the rat with a rate of 420 bpm, or 7 Hz, sampling rate should be at least 210 samples per second. Along the same lines one can reason that equipment used in hemodynamics should be sufficiently fast so that 15 times the heart rate can be accurately measured.

In practice we use a large safety factor of about 3 or 4, and therefore a sampling rate of 100 Hz is certainly sufficient for the human at rest. In exercise the sampling rate should be increased by the same factor as the increase in heart rate.

#### *Limitations*

The following limitations apply to the use of Fourier analysis [4].

1. Fourier analysis may only be performed periodic signals. In practice this means that the signal value at the start and end of the period to be analyzed should be the same. In other words only single heart beats or multiples of full beats, where start values and end values of the signals are equal may be analyzed.
2. Fourier analysis can always be performed on signals in the steady state of oscillation. However, the calculation of the relation of two signals only leads to useful results when the system is linear, which means that sine wave input leads to sine wave output. The system should also be time invariant. Despite the nonlinear relations between pressure and diameter and pressure and flow etc., in many situations nonlinearity is not so strong that large errors result. However, the scatter in modulus and phase of the input impedance has been suggested to result from nonlinearity of the arterial system [3].
3. The amplitudes of the higher harmonics decrease in amplitude and are therefore more subject to noise than the lower harmonics. Thus the high frequency information should be considered with care.
4. Fourier analysis gives data at multiples of the heart rate only. Thus the frequency resolution is limited. Pacing of the heart at different rates, including high heart rates, improves the resolution of frequency and also high frequency information.

It is also advisable to analyze a number of beats (~10) in the steady state to reduce noise [2]. This can be done by analysis per beat, and averaging the derived harmonics of these beats. It is, in principle, equally accurate to analyze a series of beats. When the heart rate is 75 bpm, i.e., 1.25 Hz, and a series of 10 beats is analyzed, harmonics are obtained at multiples of 0.125 Hz. However, only the harmonics 1.25 Hz, 2.50 Hz, etc. contain accurate information.

#### **Physiological and clinical relevance**

Fourier analysis and the subsequent calculation of the amplitude ratio and phase angle difference per harmonic of two hemodynamic signals give information about a linear and time invariant system. An example is input impedance (Chapter 23). An important other example is the calculation of the pressure transfer function (Chapter 26). When radial and aortic pressure are measured, the Fourier analysis of these two signals and subsequent calculation of their amplitude and phase relation leads to the transfer function, which describes the arterial system in between these two sites. Once the transfer function is known, radial pressure can be used to derive aortic pressure as long as the arterial system does not change.

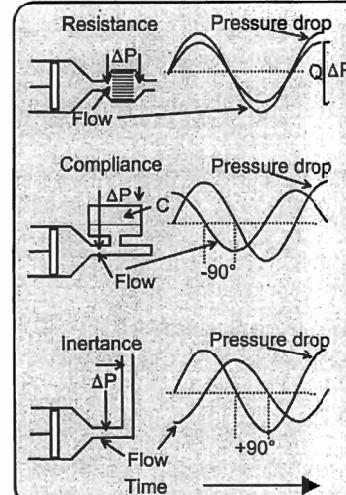
Nonlinearity of the system e.g., cardiac valves, the pressure-flow relation over a stenosis etc., does not allow calculations based on this linear approach. For instance, systemic vascular resistance and impedance can be calculated from aortic pressure minus venous pressure and aortic flow but not from ventricular pressure and flow.

The oscillatory flow theory is also based on sinusoidal relations between pressure drop over and flow through a segment of artery (Chapter 8).

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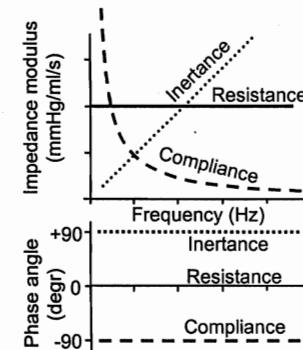
## Appendix 2 BASIC HEMODYNAMIC ELEMENTS



THE THREE BASIC HEMODYNAMIC ELEMENTS are resistance, compliance and inertance. For steady flow only resistance has a meaning. Oscillatory flow theory demands the use of sine waves. Here the relations between sinusoidal pressure drop and flow are given for the three elements. The ratio of the pressure drop and flow gives the modulus of the impedance; the phase difference between them gives the phase angle. For the resistance element pressure drop and flow are in phase, and the impedance is the resistance. For the compliance element flow precedes the pressure drop by 90 degrees and for an inertance flow lags by 90 degrees. These basic elements can, in combination, describe all oscillatory pressure-flow, and pressure-pressure relations of linear hemodynamic systems. Adapted from [1].

### Description

The impedance of the three basic hemodynamic elements is shown in the figure [1]. For the resistance, the pressure drop and flow are in phase and their amplitude ratio gives the value of the resistance. For the compliance, the sine wave of flow precedes the pressure drop, and they are 90 degrees out of phase, i.e., a quarter of the whole sine wave. The ratio of the amplitudes of the pressure drop and the flow decreases inversely with the frequency. Thus, for a flow with constant amplitude, the higher the frequency the lower the pressure is. This is formulated as follows: the modulus of the impedance,  $|Z(\omega)|$  equals  $1/\omega \cdot C$ , with  $C$  compliance and  $\omega$  the circular frequency,  $\omega = 2\pi f$ ,  $f$  being the frequency in Hz (cycles per second). Increasing frequency implies decreasing impedance modulus. The phase angle is -90 degrees for all frequencies. For the inertance the impedance modulus equals  $|Z(\omega)| = \omega \cdot L = 2\pi f \cdot L$ . Thus for a constant flow amplitude, the pressure amplitude increases with frequency. The phase angle is +90 degrees for all frequencies.



INPUT IMPEDANCE of the three basic hemodynamic elements as a function of frequency. The impedance modulus at zero Hz of inertance is negligible and of compliance is infinite.

## Physiological and clinical relevance

All linear and time invariant hemodynamic systems, for instance the entire systemic arterial tree, the pulmonary vascular system, or a pressure transfer function can be quantitatively described by a combination of these basic elements. Linear means that when the input (e.g., pressure) is a sine wave, the output (e.g., flow) should also be a sine wave.

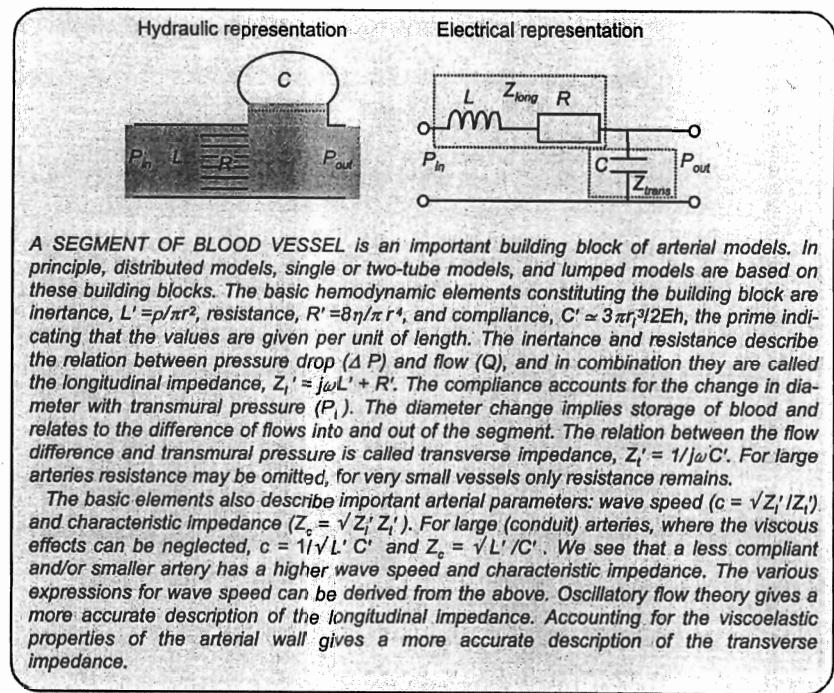
## Limitations

The arterial system is not linear. For instance, the pressure-volume relation of the arteries is not straight. Other aspects such as inlet length, curvature of vessels etc., result in nonlinear behavior. Nevertheless, in most practical aspects this non-linearity does not affect the results obtained by linear analyses much. Thus, systemic vascular resistance and aortic input impedance can be calculated and this information is meaningful. However, calculating the relation between mean and oscillatory ventricular pressure and aortic flow does not lead to useful results because of the strong nonlinearity of the aortic valves.

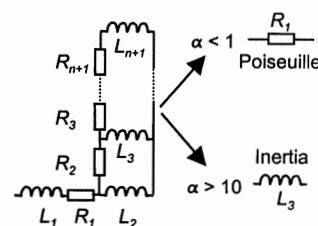
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## Appendix 3 VESSEL SEGMENT



## Description



THE LONGITUDINAL IMPEDANCE of a segment of artery in electrical terms. The ladder network results from oscillatory flow theory. For large arteries with large  $\alpha$  the inertial term is the only one of importance. Adapted from [1], used by permission.

### The longitudinal impedance

The relation between the pressure drop and flow of a uniform segment of blood vessel is given by Womersley's oscillatory flow theory and called longitudinal impedance [3]. The longitudinal impedance in electrical form is given in the figure on the next page [1]. For small arteries, i.e., for small values of Womersley's  $\alpha$ , the longitudinal impedance per unit length,  $Z'_l$ , equals  $8\eta l/\pi r^4$ . It is thus an resistance described by Poiseuille's equation. For large values of  $\alpha$ , i.e. for large arteries, the longitudinal impedance per length reduces to an inertance only, and equals  $Z'_l = i\omega\rho/\pi r^2 = i\omega\rho/A$ .

### The transverse impedance

The transmural pressure difference, i.e., the oscillatory pressure between lumen and external environment, is related to volume changes (see Chapter

## Physiological and clinical relevance

All linear and time invariant hemodynamic systems, for instance the entire systemic arterial tree, the pulmonary vascular system, or a pressure transfer function can be quantitatively described by a combination of these basic elements. Linear means that when the input (e.g., pressure) is a sine wave, the output (e.g., flow) should also be a sine wave.

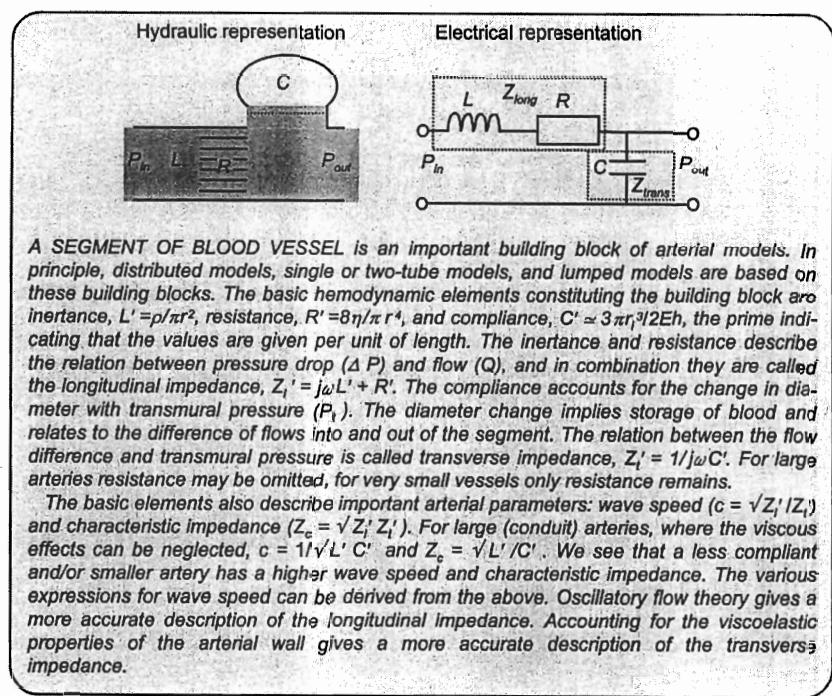
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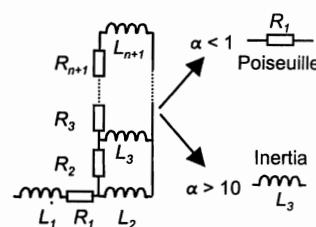
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## Appendix 3 VESSEL SEGMENT



### Description



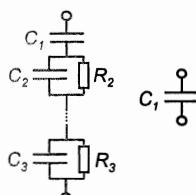
THE LONGITUDINAL IMPEDANCE of a segment of artery in electrical terms. The ladder network results from oscillatory flow theory. For large arteries with large  $\alpha$  the inertial term is the only one of importance. Adapted from [1], used by permission.

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#### The transverse impedance

The transmural pressure difference, i.e., the oscillatory pressure between lumen and external environment, is related to volume changes (see Chapter



**THE TRANVERSE IMPEDANCE** of a segment of artery in electrical form. The dashpot-spring representation is shown in Chapter 10. The ladder network results from the complex elastic modulus. Adapted from [2], used by permission.

In other words compliance is mainly located in the conduit arteries. We should remember that all three basic elements are determined not only by the material properties but also by the geometry.

#### Wave speed and characteristic impedance

Wave speed and characteristic impedance are two important blood vessel parameters characterizing its wave transmission and reflection properties. These two quantities can be derived from so-called wave transmission theory, in analogy to what happens in telegraph lines, or antenna cables, for the transmission of electromagnetic waves. We will here give a simpler approach in which we neglect the effect the viscous resistance thereby omitting the damping of waves while they travel. This approximation is permitted since wave travel and characteristic impedance are of interest only in the large conduit arteries, where the resistance effects are small.

Wave speed is the velocity with which a disturbance travels through a blood vessel. It can be pressure, flow or wall movement. The wave speed  $c = \sqrt{Z_i/Z'_i} = 1/L'C'$ . Rewriting this gives  $c = \sqrt{A \cdot \Delta P / \Delta A \cdot \rho} = \sqrt{V \Delta P / \Delta V \cdot \rho}$ . This formula of the wave speed was derived by Frank (1920), and later by Bramwell and Hill (1922). The wave speed according to Newton and Young is  $c = \sqrt{K/\rho}$  with  $K = A \Delta P / \Delta A = V \Delta P / \Delta V$ .

Using  $A = \pi r^2$  and thus  $\Delta A = 2\pi r \cdot \Delta r$ , we arrive at  $c = \sqrt{r \cdot \Delta P / 2 \Delta r \cdot \rho}$ . This form is useful in the estimation of wave speed from changes in radius and pressure. Inserting  $C' \approx 3\pi r_i^3 / 2E \cdot h$  and  $L' = \rho / \pi \cdot r^2$  leads to  $c = \sqrt{2E \cdot h / 3r \cdot \rho}$ . However, using  $\Delta P / \Delta r = h/r \cdot (\Delta \sigma / \Delta r)$ , gives  $c = \sqrt{E \cdot h / 2r \cdot \rho}$ . The difference results from the way the formula is derived, and equals the factor 1 - Poisson ratio<sup>2</sup>, with the Poisson ratio being 0.5 for incompressible wall material, this equals 3/4, and 2/3 times 3/4 equals 1/2. The difference in the square root of 2/3 and 1/2 is about 15%.

The choice of formula depends on the information desired. If local compliance is to be derived, the Frank or Bramwell-Hill equation is

11). Volume changes can be related to flow, and therefore we can use the term transverse impedance. The transverse impedance for a viscoelastic wall material is shown in the figure on the next page [2]. For large conduit arteries, where the wall is almost purely elastic, this can be simplified to a single compliance,  $C = \Delta V / \Delta P = (\Delta A / \Delta P) \cdot l$ . The compliance per unit length is then  $C' = \Delta A / \Delta P$ . The compliance element can be written in a different form using the Law of Laplace, to obtain stress from pressure, and accounting for cylindrical geometry to relate volume to radius. The expression for compliance then becomes  $C = 3\pi \cdot l \cdot r_i^2 \cdot (r_i + h)^2 / E \cdot h \cdot (2r_i + h)$ , or when  $h \ll r_i$ ,  $C \approx 3\pi r_i^3 \cdot l / 2E \cdot h$ . The transverse impedance per length is  $Z'_i = 1 / i\omega \cdot C'$ . From the formulas given in the box we see that inertance is proportional to  $r_i^{-2}$ , and resistance to  $r_i^{-4}$ . This implies that resistance increases most strongly towards the periphery and this is why it is the overriding element there. Compliance decreases towards the periphery, with  $r_i^3$ , meaning that peripheral vessels contribute little to overall compliance.

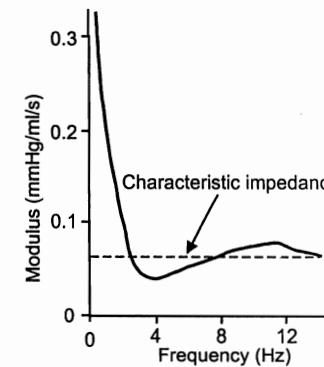
preferred. If the material constant is to be obtained the Moens-Korteweg equation is to be used.

When the heart ejects it has to accelerate the blood into a compliant aorta. Thus what the heart encounters first during ejection is the combination of the effects of compliance and inertance. Inertance increases the load but

compliance makes it easier to eject. The combined effect is given by the characteristic impedance  $Z_c = \sqrt{Z'_i Z'_i} = \sqrt{L'/C'}$ . The  $Z_c$  is called the characteristic impedance because it is characteristic for the vessel and it impedes the flow. Using the equations given above for the thin walled vessel we get:  $Z_c = \sqrt{(\rho/A) / (\Delta A / \Delta P)} = \sqrt{\Delta P / A \Delta A}$ . Since pressure and diameter are in phase the characteristic impedance of large vessels is a real, frequency independent parameter. If we take the proximal aorta as an example, the ventricle encounters, during the initial part of ejection, an impedance to flow that is the characteristic impedance of the proximal aorta. If the heart were loaded with the peripheral resistance directly the load would be much higher, because the characteristic impedance of the aorta is about 7% of systemic peripheral resistance. If the aorta were infinitely long or if no reflections would return to the heart (Chapter 21), the characteristic impedance would be the load on the heart and the pressure and flow waves would have the same shape. Thus reflections cause the differences between the wave shape of pressure and flow. It also holds that early in ejection when no reflections are returning yet from the periphery, the pressure and flow are related through the characteristic impedance. This allows calculation of characteristic impedance from the ratio of the slopes of (aortic) pressure and flow (Chapter 22).

Since, for high frequencies, corresponding to short time scales, the arterial tree approaches a reflectionless system, the input impedance at high frequencies is close to the characteristic impedance of the vessel where the impedance is determined (Chapter 23). This allows for an estimation of characteristic impedance from the modulus of the input impedance at high frequencies (figure on the right). In practice the averaged impedance modulus between the fourth to tenth harmonic is used.

It can be seen that  $c/Z_c = A/\rho$ , and with  $\rho \sim 1$  in the cgs system, it holds that  $c/Z_c = A$ . Thus, if the input impedance is determined from velocity and pressure, characteristic impedance equals wave speed.



The characteristic impedance can be estimated from the input impedance modulus at high frequencies:

$$Z_c = \text{averaged } |Z_{hi}| \text{ for harmonics 4 - 10}$$



CHARACTERISTIC IMPEDANCE can be estimated from the initial phase of ejection, where reflections are minimal:

$$Z_c = dP/dt / dQ/dt$$

## Physiological and clinical relevance

From the above we see that with smaller radius, as found towards the periphery, the importance of resistance becomes greater than inertance and compliance and in the very small arterioles only the resistance remains, 'Resistance Vessels'. In large conduit blood vessels, as the human aorta, the resistance term becomes negligible and inertance and compliance accurately describe a segment of large, conduit, artery.

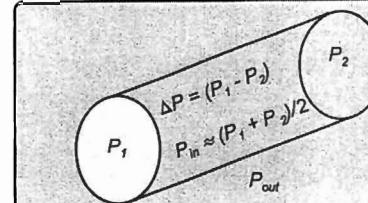
For large vessels where the wave speed is usually studied (aorta, carotid artery, and large leg and arm arteries) the resistive term is negligible so that damping of the waves is not taken into account. In these arteries there is a direct relation between the compliance and inertance with wave speed and characteristic impedance. When smaller vessels are studied the situation gets much more complex, the wave is not only transmitted but also damped.

Wave transmission is easily studied noninvasively (Chapter 20) and can give information about vessel compliance without the need to determine pressure. A decrease in aortic compliance with age by a factor of 3 increases the pulse wave velocity by about 70% ( $\sqrt{3}$ ), assuming constant radius. Decreased compliance also results in increased characteristic impedance. Both the decrease in compliance, and the increase in characteristic impedance lead to a higher pulse pressure.

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## Appendix 4 BASIC ASPECTS



THE PRESSURE DIFFERENCE along the axis,  $P_1 - P_2$ , inside the blood vessel causes the flow. The pressure inside, which is about  $(P_1 + P_2)/2$  minus the pressure outside,  $P_{\text{out}}$ , is the transmural pressure which causes the diameter increase.

### Description

#### Pressure and flow

Pressure is the force applied per unit area. In hemodynamics we always think of pressure in terms of a pressure difference. The pressure difference along the axis, or pressure gradient, is the pressure that causes the flow of blood. The pressure difference between the inside and outside of a vessel or the heart, which is often called transmural pressure, causes the wall distension.

Flow ( $Q$ ) is given in ml/s or in liters/minute (Cardiac Output). Often the terms *volume flow* or *flow rate* are used and they are here considered synonymous to the term flow. The velocity, or flow velocity of blood,  $v$ , is given in cm/s. The volume flow, and the flow velocity averaged over the cross-sectional area of a vessel are related through the cross-sectional area,  $A$ ,  $vA = Q$ .

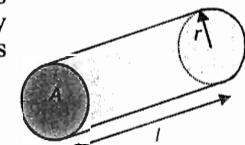
Pressure and flow result from the properties of the heart as a pump and the characteristics of the arterial system. However, the so generated pressure and flow, can be used to obtain the properties of the arterial system and the heart. For instance, aortic minus venous pressure divided by aortic flow gives total peripheral resistance. For other applications see Chapters 14 and 23.

#### Pulsatile and oscillatory pressure and flow

Pressure and flow vary during the cardiac cycle and are therefore called pulsatile pressure and flow. When pressure and flow are subjected to Fourier analysis and written as a series of sine waves (Appendix 1) we call them oscillatory pressure and flow. The zero term equals the mean value and the harmonics are the oscillatory terms. Womersley's oscillatory flow theory pertains to sinusoidal pressure-flow relations.

### Area

In the figure the two areas of a blood vessel are shown. The area  $A = \pi r^2$ , the so-called cross-sectional area, is the area where the pressure acts to cause flow. The law of Poiseuille connects the pressure gradient to flow via this area to the second power, namely to  $r^4$ . The cross-sectional area of the human aorta is about  $6 \text{ cm}^2$  and of an arteriole it is about  $30 \mu\text{m}^2$ . The total cross-sectional area of all capillaries



TWO AREAS are of importance: The cross-sectional area,  $A = \pi r^2$ , where the pressure acts to push blood forward, and the lateral area, which equals  $2\pi rl$ , and is used for exchange.

together is about  $5000 \text{ cm}^2$  or  $0.5 \text{ m}^2$ .

The lateral area or exchange area is the area involved in the exchange of oxygen, substrates and metabolites between tissue and blood. This area is calculated as:  $2\pi r \cdot l$ , with  $l$  length. The total exchange area of all capillaries together is about  $6000 \text{ m}^2$ .

#### *Wave speed differs from flow velocity*

Blood flow velocity is the speed with which the molecules and cells in the blood move from heart to periphery on the arterial side and back ('venous return') on the venous side. The, mean, velocity of blood in the aorta is about  $15 \text{ cm/s}$ , maximum velocity of blood in systole in the aorta is about  $100 \text{ cm/s}$ , and in the capillaries the average velocity is about  $0.5 \text{ mm/s}$ .

Wave speed or wave velocity is the velocity with which the pressure wave, the diameter variation and the flow wave travel. The wave speed pertains to pulsatile phenomena, and depends on vessel size and vessel elasticity (Chapter 20). The values of wave speed are between  $4$  and  $10 \text{ m/s}$ , thus much higher than the blood flow velocity.

#### *Volume, Flow and Circulation Time*

Volumes of compartments, flow and circulation time can be determined using an identifiable, nontoxic indicator that does not leave the compartment under study. Examples of indicators are dyes, radioactive tracers, or cold saline (thermodilution technique). For the last indicator a correction for disappearance from the circulation is made.

Blood volume can be determined by an intravenous injection of an amount,  $m_d$ , of a dye. The measurement of the concentration of the marker,  $[C]$ , in a blood sample, after complete mixing, allows for the calculation of the blood volume,  $V$ . When the concentration in the blood is  $[C] = m_d/V$  it follows that  $V = m_d/[C]$ . The injection may be performed in any blood vessel and the sample may be taken from any vessel as well.

Blood flow can be determined from a rapid injection of an indicator, amount  $m_d$ , and measurement of the concentration-time curve of the indicator in the blood. This is called the indicator dilution technique to determine mean flow. The flow is calculated as  $m_d/\text{area under the time-concentration curve}$ . In the indicator dilution technique, flow is determined at the location of injection, while the location of detection of the concentration-time curve is free. For instance, injection of a dye in the left atrium, guarantees good mixing, and allows for the estimation of Cardiac Output. The measurement of the concentration-time curve may take place in any artery and is thus rather free to choose.

In the indicator dilution technique cold saline is often used, and the method is then called the thermodilution technique. The most frequently used method is by flow guided catheter, injection of cold saline in the right atrium or right ventricle and measurement of the temperature in the pulmonary artery. The commercially available apparatuses correct for heat loss.

Circulation time is obtained by rapidly injecting an indicator at one location,  $x_1$ , and measurement of the arrival time at another location,  $x_2$ . Circulation time alone is of limited use but in combination with flow it allows estimation of the vascular volume between the two points. The volume of vascular bed between  $x_1$  and  $x_2$  equals the circulation time between

$x_1$  and  $x_2$  times volume flow. The circulation time of the entire circulation is about 1 minute.

#### *The Navier-Stokes equations*

The Navier-Stokes equations form the basis of all fluid dynamics, including hemodynamics, and can be found in textbooks on fluid mechanics (Appendix 5). They are the equations of motion of the fluid due to the forces acting on it such a pressure and gravity, and the equations include the effect of fluid density and viscosity. It is a group of three sub-equations, each for one of the three spatial dimensions.

The exact mathematical solution of these general equations is not possible because of their nonlinear character, so that large computers are required to solve them for each situation. The software to solve the equations is available. One of the terms representing this method is Computational Flow Dynamics.

Under simplifying assumptions the Navier-Stokes equations can be solved. Poiseuille's law, Pulsatile Flow Theory and Bernoulli's equation, etc., are examples of a straightforward derivation.