The cardiac output is the volume of blood ejected by one ventricle in one minute, and equals the stroke volume \( \times \) number of beats per minute. The need to measure human cardiac output arises in many areas of research, for example, evaluating the cardiac adaptation to physical training, and also in clinical practice, for example quantifying the severity of cardiac disease and its response to treatment.

Cardiac output can be measured as a single entity in humans using the Fick principle or the dilution method. Alternatively, stroke volume can be measured separately by Doppler ultrasound, radionuclide counting or echocardiography, and the result multiplied by heart rate to give cardiac output. The heart rate is obtained by counting the radial pulse, or by ECG, or by a pulse oximeter (see later). All the above cardiac output methods require complex technology. A much simpler and more convenient estimate, albeit rather indirect, is to measure the arterial pulse. We will begin here with the gold standard but invasive method, the Fick principle, then move in the direction of less direct but less invasive methods. The Fick principle has a wider, physiological importance, besides cardiac output measurement. It is a general principle describing the transport of any solute across a capillary bed, and is thus crucial to understanding a core role of the cardiovascular system – the uptake of \( \text{O}_2 \) in the lungs.

### 7.1 Fick's principle and pulmonary oxygen transport

Adolf Fick pointed out in 1870 that the rate at which the pulmonary capillaries take up \( \text{O}_2 \) in the lungs must equal the increase in \( \text{O}_2 \) concentration in the blood multiplied by the pulmonary blood flow. Since the pulmonary blood flow is the right ventricular output, it follows that cardiac output can be calculated from measurements of \( \text{O}_2 \) uptake.

#### Fick's principle quantifies \( \text{O}_2 \) uptake in the lungs

As noted above, Fick’s principle is more than just a method – it is basic to understanding \( \text{O}_2 \) uptake in the lungs, \( \text{CO}_2 \) elimination and many other
physiological exchanges (Figure 7.1). The amount of O\textsubscript{2} carried into the lungs per minute in venous blood equals pulmonary blood flow times venous oxygen concentration C\textsubscript{V}:

\[
\text{O}_2 \text{ in venous blood entering lungs per minute} = \dot{Q}C_V
\]

Similarly, the amount of O\textsubscript{2} carried away from the lungs per minute in the arterialized blood equals the pulmonary blood flow times the arterial oxygen concentration C\textsubscript{A}:

\[
\text{O}_2 \text{ in arterialized blood leaving lungs per minute} = \dot{Q}C_A
\]

The amount of O\textsubscript{2} taken up by the blood as it passes through the lungs is the difference between the amount of O\textsubscript{2} entering and the amount leaving, i.e.:

\[
\text{O}_2 \text{ uptake by pulmonary blood per minute} = \dot{Q}C_A - \dot{Q}C_V
\]

In the steady state, the amount of O\textsubscript{2} taken up by the blood per minute must equal the amount of O\textsubscript{2}

\[
\text{O}_2 \text{ removed from the lung alveolar gas per minute, } \dot{V}_{O_2}
\]

so we can write:

\[
\text{O}_2 \text{ removal from alveolar gas} = \dot{V}_{O_2} \text{ uptake by pulmonary blood}
\]

or in symbols:

\[
\dot{V}_{O_2} = \dot{Q}C_A - \dot{Q}C_V
\]

Re-expressing this in terms of the O\textsubscript{2} arteriovenous concentration difference C\textsubscript{A} - C\textsubscript{V}:

\[
\dot{V}_{O_2} = \dot{Q}(C_A - C_V)
\]

This is the Fick equation. It tells us that the rate of O\textsubscript{2} uptake from the inspired air, in ml O\textsubscript{2}/min, equals pulmonary blood flow (in litre/min) multiplied by the arteriovenous difference in O\textsubscript{2} concentration (in ml O\textsubscript{2}/litre blood).

Since the pulmonary blood flow \dot{Q} is the right ventricular output, we can rearrange the Fick equation to work out the cardiac output, thus:

\[
\text{Cardiac output } \dot{Q} (l/min) = \frac{\text{Oxygen uptake rate } V_{O_2} (ml/min)}{\text{ArterialO}_2 \text{ conc } C_A - \text{VenousO}_2 \text{ conc } C_V (ml/l)}
\]

An example should make this clear. A resting human absorbs \sim 250 ml O\textsubscript{2} per minute from the alveolar gas (\dot{V}_{O_2}). Arterial blood contains 195 ml O\textsubscript{2} per litre and the mixed venous blood entering the lungs contains 145 ml O\textsubscript{2} per litre; so each litre of blood takes up 50 ml O\textsubscript{2} as it passes through the alveoli, i.e. (C\textsubscript{A} - C\textsubscript{V}) = 50 ml/l. To take up 250 ml O\textsubscript{2}, 5 litres of blood are required (250/50). This amount of O\textsubscript{2} is taken up in 1 min. Right ventricular output is therefore 5 litres/min.

Fick’s method requires cardiac catheterization

Fick’s method only became practicable in humans in the twentieth century, when the advent of cardiac catheterization enabled mixed venous blood sampling from the right ventricle/pulmonary trunk. Mixed venous blood analysis tells us the average O\textsubscript{2} concentration entering the lungs. Peripheral venous blood is no good for this purpose, because its O\textsubscript{2} concentration varies markedly between tissues, e.g. renal venous O\textsubscript{2} 170 ml/l, coronary venous O\textsubscript{2} 70 ml/l. The different streams of venous blood only become fully mixed in the right ventricle.
The difficult problem of sampling mixed venous blood in humans was solved by the German physician Werner Forssman, who in 1929 passed a ureteric catheter up his own arm vein into the right heart, watching its progress on an X-ray screen. This brave act founded human cardiac catheterization, won Forssman the disapproval of his head of department and, later, a Nobel prize.

The Fick method is now applied as follows. The subject’s resting O₂ consumption, $V_{O_2}$ is measured for 5–10 min by spirometry, or by collecting expired air in a Douglas bag. During this period an arterial blood sample is taken from the brachial, radial or femoral artery, and a mixed venous sample is taken from the right ventricle outflow tract/pulmonary trunk, using a cardiac catheter introduced through the antecubital (elbow) vein. The O₂ content of each blood sample is measured and the cardiac output calculated as above.

The Fick method has several limitations

Although the Fick method is the yardstick by which new methods are judged, it has its limitations. The O₂ uptake measurement takes 5–10 min to perform, so beat-by-beat changes in stroke volume cannot be resolved. Also, the method is only valid in the steady state, so a rapidly changing cardiac output cannot be measured. Being invasive, the method is inadvisable during hard exercise, because the cardiac catheter may trigger an arrhythmia in a violently beating heart. The indirect Fick method avoids cardiac catheterization and estimates $C_V$ indirectly, by the analysis of re-breathed gas – an approach used recently in an orbiting space laboratory.

The Fick principle has many applications

The Fick principle is an important, general physiological principle that applies to the exchange of any material in any perfused organ – for example, glucose transport from blood to skeletal muscle or the brain (Section 10.10). The Fick principle even applies to heat exchange in a water-perfused radiator, or money turnover at the turnstile of a football ground (Figure 7.1b). In general terms, the transfer rate, $J$, of any substance between a flowing body and its surroundings equals the flow $Q$ multiplied by the concentration difference between the incoming fluid, $C_{in}$, and the outgoing fluid, $C_{out}$:

$$J = Q(C_{out} - C_{in})$$  (7.2)

The Fick principle has therefore been used to work out the rate at which an organ consumes a metabolite, such as glucose, based on measurements of local blood flow and arteriovenous concentration difference.

### 7.2 Indicator and thermal dilution methods

The thermal dilution method has been much used in cardiology departments, but we will first consider its parent, the indicator dilution method, which is easier to understand.

**Indicator dilution method**

A known mass of a foreign substance, the indicator, is injected rapidly into a central vein or the right heart. It is necessary that the indicator is confined to the bloodstream and easy to assay, such as dyes that bind to plasma albumin (Evans blue, indocyanine green), radiolabelled albumin or radiolabelled red cells. The indicator becomes diluted in the venous bloodstream, then carried through the heart and lungs and ejected into the systemic arteries (Figure 7.2a). Systemic arterial blood is sampled from the radial or femoral artery, and its indicator content is plotted against time.

For simplicity, let us first suppose that the ejected bolus of arterial blood has a uniform concentration of the indicator (Figure 7.2b). The concentration versus time plot tells us two things: the time taken by the labelled bolus to pass a given point and the average concentration of indicator in the bolus. Concentration $C$ is by definition the injected mass $m$ divided by the volume of plasma in which the indicator has become distributed, $V_D$; in other words, $C = m/V_D$. The distribution volume of the indicator is thus:

$$V_D = m/C$$

For example, if 1 mg of indicator produced a mean plasma concentration of 1 mg/l, its volume of distribution must be 1 litre. If this volume takes $t$ seconds to pass the sampling point, the left ventricle must be ejecting plasma at the rate $V_D/t$. In Figure 7.2b, the rate is 1 litre in 20 s, or 3 l/min. Thus the plasma output is:

$$\text{Cardiac output (plasma)} = \frac{V_D}{t} = \frac{\text{Mass of indicator}, m}{\text{Mean concentration}, C} \times \frac{\text{passage time}, t}{1 - \text{haematocrit}}$$

The output of blood is the plasma output divided by $1 - \text{haematocrit}$; the haematocrit is the fraction of the blood that is made up of red cells (0.40–0.45).
7.2 Indicator and thermal dilution methods

This simplification is very helpful, because in reality the arterial concentration is not constant (Figure 7.2c, cf. 7.2b) – but we can still measure the area under the curve. The concentration rises to a peak, after which it decays exponentially, because the ventricle only ejects about two-thirds of its contents per systole. The residual indicator in the ventricle is diluted by indicator-free venous blood returning during the next diastole, and the diluted blood is in turn only partially ejected in systole and so on.

After about 15 s the concentration decay curve is interrupted by a recirculation hump – the asterisk in Figure 7.2c. This is caused by blood with a high indicator content returning to the heart after one complete transit of the myocardial circulation, which is the shortest, quickest circulation in the body. To use the area equation, we need to work out the area under the curve excluding the recirculation hump. To this end, the pre-hump part of the decay curve is extrapolated underneath the recirculation hump. A semilogarithmic plot converts the exponential decay into a straight line, which can then be extrapolated under the hump to a negligible concentration (usually 1% of the peak), as in Figure 7.2c. The area under the corrected $C$ versus $t$ curve is used to calculate the cardiac output.

A modern, computerized version of the method is based on intravenous lithium ion injection. The lithium can be detected in the arterial blood by an ion-sensitive electrode. It appears that lithium loss during passage through the lungs is negligible.

Pros and cons of the indicator dilution method

The indicator dilution method agrees with the Fick method to within 5%. The dilution method has a better time resolution (30 s) than the Fick method (5–10 min). Also, it can be used in exercise, since there is no need for ventricular catheterization. The error involved in extrapolating the decay curve is, however, a drawback, and becomes a serious limitation in diseased hearts, where the initial part of the decay curve may be short and distorted.

Thermal dilution method

This variant method has been used widely in cardiac departments, owing to its greater convenience. Instead of a soluble indicator, temperature is used. A thermistor (temperature sensor) at the tip of a Swan–Ganz catheter is advanced into the pulmonary trunk/artery. A known mass of cold saline is then injected quickly into the right atrium, right
ventricle or proximal pulmonary trunk. The distal thermistor records the dilution of the cold saline by the warm pulmonary bloodstream. Cardiac output is calculated as the injected amount of heat (i.e. cold) divided by the area under the temperature–time plot.

**Pros and cons of thermal dilution**

The major advantage of thermal dilution over indicator dilution is that it circumvents the recirculation hump problem, because the cold saline has warmed up to body temperature by the time it recirculates to the right ventricle. Heat transfer across the walls of the right ventricle and pulmonary artery can cause an overestimation of the distribution volume and hence cardiac output, but a computed correction is made for this.

### 7.3 Aortic flow by pulsed Doppler method

To estimate left ventricular stroke volume, pulses of ultrasound are directed down the ascending aorta from a transmitter crystal placed over the suprasternal notch (Figure 7.3, top). The moving red cells alter the frequency of the ultrasound reflected off them, and the frequency shift is proportional to the red cell velocity. This is called the Doppler shift, and is analogous to the change in pitch of a police car siren as it speeds past. The reflected ultrasound is recorded and used to compute the mean blood velocity across the aorta, millisecond by millisecond. The mean aortic blood velocity is plotted against time (Figure 7.3, bottom), and interpreted as follows.

**Stroke distance is distance advanced along the aorta per ejection**

Since distance is velocity × time, the distance that blood advances along the aorta during one systole, the stroke distance, equals the area under the aortic velocity–time curve. To convert stroke distance into stroke volume, the cross-sectional area of the aorta is measured by echocardiography (see Section 2.6). The area, in cm², multiplied by stroke distance in cm, gives stroke volume in cm³, less the volume drained off by the coronary arteries.

**Pros and cons of Doppler method**

The Doppler method is difficult to calibrate and has noise problems. But it has two enormous advantages – it is non-invasive and has an extremely high temporal resolution, recording every instant of ejection, unlike the Fick or dilution methods.

### 7.4 Peripheral pulse and its relation to cardiac output

The oldest, cheapest, quickest and easiest way to assess human cardiac output is to palpate the radial pulse at the wrist. **Heart rate** can be counted and the **strength of the pulse** can be estimated subjectively. A strong pulse is the result of a large stroke volume, for example during exercise; and a weak pulse is the result of a low stroke volume, for example after a haemorrhage. What the finger actually detects is the expansion of the artery as pressure rises during systole. The rise in pressure, or **pulse pressure**, equals systolic pressure minus the diastolic pressure. Pulse pressure is easily quantified by sphygmomanometry (Section 8.5), and is closely related to stroke volume, as follows.

**Stroke volume and pulse pressure are linked by arterial compliance**

The relation between left ventricular stroke volume and systemic arterial pressure is one of the key haemodynamic relations of the circulation. It is introduced here, and is analysed in more detail in...
Chapter 8. During ejection, most of the stroke volume (70–80% at rest) is accommodated in the elastic arteries, because the ventricle ejects blood faster than it can drain away through the resistance vessels. The increase in arterial volume distends the arteries, and the arterial wall tension raises the blood pressure (Figure 7.4). The magnitude of the increase in pressure, or pulse pressure, thus depends on the stroke volume and the compliance (distensibility) of the arterial system. Compliance is defined as change in volume per unit change in pressure:

\[
\text{Arterial compliance} = \frac{\text{Increase in blood volume}}{\text{Increase in arterial pressure}}. \tag{7.3}
\]

Arterial compliance in a young adult is \(\sim 2\, \text{ml per mmHg}\) at normal blood pressure. The increase in arterial blood volume during systole equals stroke volume minus the volume that drains away during the ejection period (runoff). Inserting this statement into the top line of 7.3 and rearranging, we see that the increase in arterial pressure per heart beat, the pulse pressure, is related to stroke volume as follows:

\[
\text{Pulse pressure} = \frac{\text{Stroke volume} - \text{runoff in systole}}{\text{Arterial compliance}}. \tag{7.4}
\]

Changes in pulse pressure can thus serve as a guide to changes in stroke volume. In intensive care units, pulse pressure in the finger is monitored continuously, and the data are processed by computer, based on eqn 7.4, to display a beat-by-beat estimate of stroke volume, heart rate and cardiac output.

**Arterial compliance is not a fixed quantity**

A significant problem when interpreting pulse pressure is that arterial compliance does not have a unique, unchanging value; its magnitude varies, as follows:

- Arterial compliance falls (stiffness increases) as pressure and volume increase; so the arterial pressure–volume plot is a steepening curve (Figure 7.4c).
- Arterial compliance is reduced by high ejection velocities, because the artery wall is a visco-elastic material, and takes time to relax (see Appendix 2). During exercise the pulse pressure increases relatively more than the stroke volume, because there is less time for viscous relaxation of the wall during a fast ejection.
- Arterial compliance declines with age, due to a degenerative stiffening of elastic arteries called arteriosclerosis. Consequently, pulse pressure increases with age, and this increases stroke work.

---

**Arterial compliance links pulse pressure and stroke volume**

- Compliance is a measure of distensibility; it is the inverse of stiffness. Arterial compliance \(C\) is defined as the increase in blood volume in the arterial system, \(\Delta V\), required to produce unit increase in arterial pressure, \(\Delta P\). Thus \(C = \Delta V/\Delta P\).
- Pulse pressure is the increase in pressure between diastole and systole.
- From the above definitions, pulse pressure \(\Delta P = \text{stroke volume (minus the runoff during ejection)/arterial compliance}\). Pulse pressure can thus be increased by a rise in stroke volume (e.g. exercise) or a fall in arterial compliance (e.g. ageing).
- Arterial compliance falls as pressure increases, due to the tensing of collagen in the artery wall. Consequently, a rise in mean arterial pressure also causes a rise in pulse pressure.
- Arterial compliance declines with age due to arteriosclerosis, a diffuse stiffening of the media of elastic vessels. As a result pulse pressure can double between youth and old age.
Arteriosclerosis is the diffuse stiffening of ageing elastic arteries, due primarily to changes in the tunica media. It should not be confused with atheroma, which is primarily a cholesterol-related disease of the tunica intima (Table 17.4).

Pros and cons of pulse method

- The variable nature of arterial compliance can introduce some ambiguity, as can runoff during ejection, since runoff increases when peripheral resistance falls. Nevertheless, changes in pulse pressure, recorded with nothing more sophisticated than a wrist watch and sphygmomanometer cuff, offer a convenient, instant, bedside indication of changes in cardiac output in an individual from hour to hour, for example during recovery from an acute haemorrhage. At a more sophisticated level, computer models make reasonably accurate computations of acute changes in stroke volume from continuous recordings of peripheral arterial pressure. The latter can be measured continuously by an electronic, finger-volume clamp method (see Finapress, Section 8.5). This has enabled continuous computer monitoring of stroke volume, heart rate and cardiac output in intensive care units.

Pulse oximetry monitors pulse rate

- The heart rate can be measured using a watch and palpation of the radial artery; or a miniaturized ECG that transmits the heart rate to a wrist monitor, or a pulse oximeter. An oximeter is a small device that shines a light through superficial tissue, usually an ear lobe or finger, and measures the transmitted light, using a photodiode cell. Red cells absorb some of the light, and oxyhaemoglobin absorbs a different wavelength to deoxyhaemoglobin. As the arterial system expands with each pulse, the light transmission changes. From this the pulse rate and blood oxygen saturation are computed.

7.5 Radionuclide ventriculography, echocardiography and other methods

Radionuclide ventriculography

A gamma-emitting radionuclide, usually a technetium-99 compound bound to red cells, is injected intravenously, and a precordial gamma camera records the gamma counts emanating from the ventricles. The difference between the radioactive content of the ventricles in diastole and systole is used to calculate the ejection fraction and stroke volume. The method requires, obviously, the services of a nuclear medicine department.

Quantitative echocardiography (ultrasound cardiology)

Echocardiography is non-invasive, and can measure the end-diastolic and end-systolic dimensions of the ventricle (Figures 2.9 and 6.24). The stroke volume and ejection fraction are then computed from the linear dimensions, using an assumed chamber geometry. Typical values are listed in Table 2.2. Magnetic resonance imaging (MRI) of the cardiac chambers can be used in a similar way.

Impedance cardiology

Chest and neck leads pass a small current through the thorax, to measure its cyclically changing electrical resistance (impedance). Aortic blood volume increases and decreases over each cardiac cycle, and since blood is a better conductor than air, the electrical impedance of the thorax oscillates likewise. Aortic stroke volume can be estimated, albeit rather indirectly, from the impedance oscillation. The method is non-invasive, but very indirect.

Electromagnetic ‘flow’ meter

This method is invasive, and is only used in laboratory animals for research purposes. Under general anaesthesia a miniature, semicircular magnet is surgically implanted, with its magnetic poles on either side of the blood vessel of interest, e.g. pulmonary artery. Blood is an electrical conductor, and as it cuts through the magnetic field it induces an electrical potential, which is measured. The potential is proportional to the blood velocity (cm/s), not flow. To convert mean velocity to flow, the internal diameter of the vessel is required. Being small, an electromagnetic flowmeter can be left inside a conscious animal, transmitting a signal by telemetry (radio-waves). In this way, much has been learned about the regulation of stroke volume in unfettered, conscious animals, such as dogs running on a treadmill.
**SUMMARY**

- The gold standard method for measuring human cardiac output is the Fick principle. This states that solute transfer rate = blood flow × concentration difference between incoming and outgoing blood. \(O_2\) uptake in the lungs is measured over 5–10 min by spirometry or expired air collection. The \(O_2\) content of mixed venous blood is measured in a blood sample taken from the right ventricle by cardiac catheterization. Arterial blood is sampled from a systemic artery. Pulmonary blood flow, i.e. right ventricular output, is then calculated from the Fick equation above.

- **Indicator dilution** and **thermal dilution** methods have a better time resolution. A known mass of dye or cold saline is injected quickly into the right heart, and the concentration or temperature is recorded at a point downstream. Concentration or temperature is plotted versus time. Knowing the injected mass \(m\), and the average downstream concentration \(C\) (or temperature), the volume of blood in which the indicator has distributed can be calculated; \(V_D = m/C\). Volume \(V_D\) is divided by the time taken for the labelled blood to pass the sampling point. This equals the cardiac output.

- **Pulsed Doppler ultrasound** measures the average blood velocity across the aorta, millisecond by millisecond. The area under the velocity–time plot gives the distance advanced per ejection (stroke distance). Stroke volume is stroke distance × aortic diameter, which is measured by ultrasound.

- **Radionuclide ventriculography** measures the radioactive counts present in the ventricle during end-diastole and end-systole. The stroke volume and ejection fraction are calculated from the difference between counts.

- **Echocardiography** (ultrasound cardiology) records the changes in ventricular dimensions between diastole and systole, to estimate stroke volume and ejection fraction.

- With all methods that estimate stroke volume, the cardiac output is calculated as heart rate × stroke volume. The pulse rate can be monitored by **pulse oximetry** or **ECG**.

- **Peripheral pulse examination** is the simplest bedside method for assessing cardiac output. Heart rate is determined by counting the pulse. Sphygmonanometry measures the pulse pressure (systolic minus diastolic pressure). **Pulse pressure** is proportional to stroke volume, although the relation is complicated by runoff, non-linear aortic compliance, dependence on ejection rate and age-related arterial stiffening (arteriosclerosis). A computerized, continuous display of cardiac output based on finger pulse monitoring is used in intensive care units.

---

**Further reading**


Mehta N, Iyawe VI, Cummin ARC, Bayley S, Saunders KB, Bennett ED. Validation of a Doppler technique for beat-to-beat measurement of cardiac output. *Clinical Science* 1985; **69**: 377–82.

