

# Levick's Introduction to Cardiovascular Physiology

Sixth Edition

**Neil Herring and  
David J. Paterson**



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Introduction to  
**Cardiovascular  
Physiology**

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# Introduction to Cardiovascular Physiology

Sixth Edition

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We dedicate this book to our pupils and teachers and the British Heart Foundation  
who have supported our research

We shall not cease from exploration, and the end of all our exploring will be to arrive where we started and know the place for the first time.

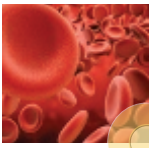
*T. S. Eliot*



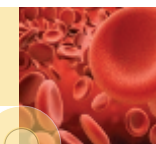
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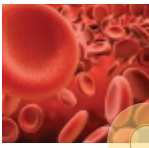




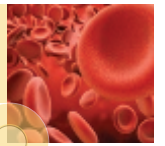
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# Foreword

The seventeenth century physician William Harvey is known for his treatise on the motion of the heart and blood which was published in *De Motu Cordis et Sanguinis* in 1628. Harvey's description of experiments on many species unequivocally dispelled the long-held Galenic dogma that blood passed from the right side of the heart to the left through invisible pores in the ventricular septum. Harvey, using the scientific method, proved there were no such pores and that blood had to move in a circular fashion. He showed that the amount of blood pumped by the heart per minute was many times the volume of blood. Harvey wrote

*...I found the task so truly arduous... that I was almost tempted to think... that the movement of the heart was only to be comprehended by God. For I could neither rightly perceive at first when the systole and when the diastole took place by reason of the rapidity of the movement...*

Anyone who has watched the heart beat, has placed a catheter in an artery or has recorded electrical activity of the heart cannot be anything other than awestruck by the power and complexity of the heart and circulation. It is, indeed, as Harvey wrote an almost spiritual experience. Interestingly, William Harvey was Warden of Merton College at Oxford University in 1645; the same institution where Professors Paterson and Herring now reside.

The publication of the sixth edition of *Introduction to Cardiovascular Physiology* continues a rich tradition of education in cardiovascular science at Oxford. This edition is more than just an introductory textbook. It is, in our opinion, one of the most well-written and well-organized cardiovascular textbooks ever published. It is comprehensive in its scope and at the same time elegant in its simplicity.

This book covers every aspect of the heart and circulatory system. Chapters build on the anatomical, biophysical, molecular and cellular underpinning of function, to the integrative nature of each component of cardiovascular regulation. Objectives are clearly laid out, experimental evidence is highlighted, technical advances are discussed and the clinical

relevancy of each component is nicely woven into the fabric of the book. One of most outstanding aspects of this text are the figures, which are both drawn *de novo* and are modified from existing research and review publications. Figures are vibrant and well described. They help to bring the reader along a logical sequence in understanding the progression and complexity of each component.

Clearly, the book is not a novel by any means, but in reading this text, one wonders how it will end. The authors pull the physiological concepts presented in [chapters 1–16](#) together with two additional chapters devoted to adaptive responses of the cardiovascular system to environmental stimuli, exercise, aging and pathological situations. [Chapter 19](#) and [20](#) focus on the experimental approach and modern techniques in cardiovascular research. Importantly, the denouement of the scientific discussions is the section on clinical case scenarios and problem-based learning, an excellent way for medical students to utilize prior information to understand the scientific rationale underpinning diagnosis and therapeutics.

This book should be part of the library of every medical student and physiology graduate student, even if their major interest is not cardiovascular science. In our opinion, there is no better compendium of basic cardiovascular function than Levick's sixth edition. We are certain that this book will surely entice young readers and new entrants in the field to seriously consider a career in cardiovascular medicine and science!

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# Preface

The first edition of *An Introduction to Cardiovascular Physiology* by Rodney Levick was published in 1990 and has been an invaluable textbook for generations of medical and biomedical science students. Over the years, we have used its many editions extensively and with great fondness as both students and teachers. We were therefore honoured to be asked to take this textbook forward into its sixth edition. Given Professor Levick's huge contribution to this work, we have renamed the sixth edition as *Levick's Introduction to Cardiovascular Physiology*.

One of the first things we did when embarking on this task, was to consult a broad group of peers and students about what they thought of the previous edition. The striking and consistent finding was that the textbook was much loved and required 'evolution rather than revolution'. Nevertheless, we have introduced several key changes. The content has been widely updated given recent advancements, particularly in [chapters 4, 5, 9, 12, 13, 15, 16, 17 and 18](#), and the clinical cases. Although this is a textbook of cardiovascular physiology rather than pathology, it is hard to ignore the significant progress in the areas of arrhythmias, hypertension and heart failure, and we have highlighted how this has improved our understanding of the underlying physiology. We are very grateful to Dr Julian Ormerod, and Associate Professors Ian Le Grice, Keith Dorrington, Pawel Swietach, Paolo Tammaro, and Professors Kim Dora, Chris Garland, Jeff Ardell, Bruce Smaill Peter Kohl and David Eisner for their help in this regard, although any inaccuracies remain our own. We are also grateful to Dr Nikant Sabharwal, Dr Jim Newton, and

Associate Professors Oliver Rider and Rajesh Kharbanda for providing clinical images from the Oxford Heart Centre. We have updated the references for every chapter, and while the focus is on reviews from leading experts in the field, we have included classical original research papers throughout. References are now ordered with the most contemporary reviews and studies cited first. By popular demand, the figures and illustrations are now in full colour throughout the book.

The biggest change we have made is the addition of two substantial new chapters ([19 and 20](#)). There is a vast gulf to be bridged between reading a traditional textbook and reading original research papers, as required when undertaking a bachelor's degree in medical science, research dissertation or a higher research degree. It is overcoming this hurdle that students consistently find the most difficult aspect of their education. The aim of [chapters 19 and 20](#) is to introduce students to the experimental approach and design, and simply describe the increasingly complex techniques that are used in cardiovascular research as well as their advantages and limitations. We hope that this will widen the book's use and audience, and build on the outstanding foundations it has provided in teaching cardiovascular physiology over the last 28 years.

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February 2018*





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# A note on active and problem-based learning



One may read a textbook and gain a primary level of understanding of its subject; however, to master the subject thoroughly *active, 'hands-on' engagement with the subject matter is essential*. In other words, *self-expression* is vital. One may think one knows the subject, but there is nothing like verbalizing and answering questions to promote learning. To this end, learning objectives are given at the start of each chapter, and five clinical cases, with questions and answers, are included at the end of the book.

## USING THE LEARNING OBJECTIVES

---

Active learning is traditionally promoted by essay writing and question and answer tutorials. The *learning objectives* at the start of each chapter can be used as short-notes questions (e.g. 'draw and explain a delayed afterdepolarization', [Chapter 3](#)). The sections containing the answers are cited after each learning objective. Another excellent way to learn actively

is to write brief notes on each learning objective. The notes will prove invaluable when revising for examinations.

## PROBLEM-BASED LEARNING

---

To encourage active learning and clinical relevance, medical schools increasingly base teaching on clinical cases, although this has serious drawbacks, as well as advantages, in the early years. Clinical cases are challenging, because they bring together many different topics and cut across many different chapters of the book. For example, heart failure (Case 1) involves altered cardiac excitation–contraction coupling ([Chapters 3 and 18](#)), the Frank–Starling law of the heart ([Chapter 6](#)), haemodynamics ([Chapter 8](#)), microvascular fluid exchange ([Chapter 11](#)) and extrinsic control of the circulation ([Chapter 14](#)). Clinical cases are therefore presented at the end of the book, with questions and answers linked to the main text.



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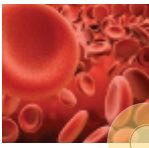
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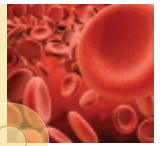
## List of abbreviations

<b>20-HETE</b>	20-hydroxyeicosatetraenoic acid	<b>CRTD</b>	cardiac resynchronization defibrillator
<b>5HT</b>	5-hydroxytryptamine	<b>CRTP</b>	cardiac resynchronization therapy pacemaker
<b>AAV</b>	adeno-associated virus	<b>CSF</b>	cerebrospinal fluid
<b>ABP</b>	arterial blood pressure	<b>CT</b>	computed tomography
<b>ABPI</b>	ankle-brachial pressure index	<b>CVLM</b>	caudal ventrolateral medulla
<b>ACE</b>	angiotensin-converting enzyme	<b>CVP</b>	central venous pressure
<b>ACh</b>	acetylcholine	<b>CVS</b>	cardiovascular system
<b>ADH</b>	antidiuretic hormone	<b>DAD</b>	delayed afterdepolarization
<b>ADP</b>	adenosine diphosphate	<b>DAG</b>	diacylglycerol
<b>AF</b>	atrial fibrillation	<b>DAPI</b>	4',6-diamidino-2-phenylindole
<b>AHN</b>	anterior hypothalamic nucleus	<b>DD</b>	diastolic depolarization
<b>Ang II</b>	angiotensin II	<b>DIC</b>	differential interference contrast
<b>ANP</b>	atrial natriuretic peptide	<b>DMNV</b>	dorsal motor nucleus of the vagus
<b>ANS</b>	autonomic nervous system	<b>DRG</b>	dorsal root ganglion
<b>AP</b>	arterial pressure	<b>dsRNA</b>	double-stranded RNA
<b>ARB</b>	angiotensin receptor blocker	<b>EAD</b>	early afterdepolarization
<b>AT</b>	atrial tachycardia	<b>ECG</b>	electrocardiogram
<b>AT1R</b>	angiotensin II receptor type 1	<b>EDD</b>	end-diastolic dimension
<b>ATP</b>	adenosine triphosphate	<b>EDH</b>	endothelium-dependent hyperpolarization
<b>AV</b>	atrioventricular	<b>EDHF</b>	endothelium-derived hyperpolarizing factor
<b>AVA</b>	arteriovenous anastomosis	<b>EDP</b>	end-diastolic pressure
<b>aVF</b>	augmented Vector Foot	<b>EDV</b>	end-diastolic volume
<b>aVL</b>	augmented Vector Left	<b>EET</b>	epoxyeicosatrienoic acid
<b>AVNRT</b>	atrioventricular nodal re-entry tachycardia	<b>EJP</b>	excitatory junction potential
<b>aVR</b>	augmented Vector Right	<b>ELISA</b>	enzyme-linked immunosorbent assay
<b>AVRT</b>	atrioventricular re-entry tachycardia	<b>EMG</b>	electromyogram
<b>BK<sub>Ca</sub></b>	large or big conductance Ca <sup>2+</sup> -dependent K <sup>+</sup> channel	<b>ENaC</b>	epithelial Na <sup>+</sup> channel
<b>BNP</b>	brain natriuretic peptide	<b>eNOS</b>	endothelial nitric oxide synthase
<b>BP</b>	blood pressure	<b>EPAC1</b>	exchange protein directly activated by cAMP 1
<b>CaMKII</b>	Ca <sup>2+</sup> -calmodulin-dependent protein kinase II	<b>ESC</b>	embryonic stem cell
<b>cAMP</b>	cyclic adenosine monophosphate	<b>ESD</b>	end-systolic dimension
<b>Cas</b>	CRISPR-associated system	<b>ESV</b>	end-systolic volume
<b>CCP</b>	critical closing pressure	<b>ET</b>	endothelin
<b>CeBF</b>	cerebellar blood flow	<b>FOXC2</b>	forkhead box protein C2
<b>CFP</b>	cyan fluorescent protein	<b>FRET</b>	Förster resonance energy transfer
<b>cGMP</b>	cyclic guanosine monophosphate	<b>GA</b>	general anaesthetic
<b>CGRP</b>	calcitonin gene-related peptide	<b>GAG</b>	glycosaminoglycan
<b>CICR</b>	Ca <sup>2+</sup> -induced calcium release	<b>GDP</b>	guanosine diphosphate
<b>CNP</b>	C-type natriuretic peptide	<b>GFP</b>	green fluorescent protein
<b>CO</b>	cardiac output	<b>GI</b>	gastrointestinal
<b>COP</b>	colloid osmotic pressure	<b>G<sub>i</sub></b>	inhibitory GTP-binding protein
<b>COX</b>	cyclooxygenase	<b>GP</b>	glycoprotein
<b>CRAC</b>	Ca <sup>2+</sup> -release activated channel	<b>GPCR</b>	G protein-coupled receptor
<b>CRISPR</b>	clustered regularly interspaced short palindromic repeats	<b>gRNA</b>	guide RNA
<b>crRNA</b>	CRISPR RNA	<b>G<sub>s</sub></b>	stimulatory guanosine triphosphate-binding protein
		<b>GTN</b>	glyceryl trinitrate



## List of abbreviations

<b>GTP</b>	guanosine triphosphate	<b>NAd</b>	noradrenaline
<b>HCN</b>	hyperpolarization-activated cyclic nucleotide-gated	<b>NAME</b>	nitroarginine methyl ester
<b>HCN4</b>	hyperpolarization-activated cyclic nucleotide-gated 4	<b>NANC</b>	non-adrenergic, non-cholinergic
<b>HDL</b>	high-density lipoprotein	<b>NET1</b>	norepinephrine transporter 1
<b>HEK 293</b>	human embryonic kidney cells 293	<b>NET2</b>	norepinephrine transporter 2
<b>HF-PEF</b>	heart failure with preserved ejection fraction	<b>NF</b>	natriuretic factor
<b>HIF-1</b>	hypoxia inducible factor 1	<b>NO</b>	nitric oxide
<b>HIP</b>	hydrostatic indifferent point	<b>NOAC</b>	novel oral anticoagulant
<b>HIT</b>	high-intensity training	<b>NOS</b>	nitric oxide synthase
<b>HPV</b>	hypoxic pulmonary vasoconstriction	<b>NOS1-AP</b>	nitric oxide synthase adaptor protein
<b>HR</b>	heart rate	<b>NP</b>	natriuretic peptide
<b>HRE</b>	HIF responsive element	<b>NPY</b>	neuropeptide Y
<b>IAP</b>	intra-abdominal pressure	<b>NTS</b>	nucleus tractus solitarius
<b>ICA</b>	internal carotid artery	<b>NZGH</b>	New Zealand genetically hypertensive (rat)
<b>ICC</b>	intercellular cleft	<b>OVLT</b>	organum vasculosum lamina terminalis
<b>ICD</b>	implantable cardioverter defibrillator	<b>P<sub>A</sub></b>	arterial pressure
<b>ICP</b>	intracranial pressure	<b>PaCO<sub>2</sub></b>	partial pressure of CO <sub>2</sub>
<b>ICS</b>	intercostal space	<b>PAF</b>	platelet-activating factor
<b>IK<sub>Ca</sub></b>	intermediate-conductance K <sub>Ca</sub>	<b>PAG</b>	periaqueductal grey
<b>IL-1<math>\beta</math></b>	interleukin-1 $\beta$	<b>PAH</b>	para-aminohippuric acid
<b>IML</b>	intermediolateral nucleus	<b>PaO<sub>2</sub></b>	partial pressure of O <sub>2</sub>
<b>IOI</b>	integrated optical intensity	<b>PAO<sub>2</sub></b>	arterial PaO <sub>2</sub>
<b>IP<sub>3</sub></b>	inositol 1,4,5 trisphosphate	<b>P<sub>C</sub></b>	capillary pressure
<b>iPSC</b>	induced pluripotent stem cell	<b>PCI</b>	percutaneous coronary intervention
<b>ITP</b>	intrathoracic pressure	<b>PCR</b>	polymerase chain reaction
<b>JAM</b>	junctional adhesion molecule	<b>P<sub>d</sub></b>	diastolic artery pressure
<b>JGA</b>	juxtaglomerular apparatus	<b>PDE2</b>	phosphodiesterase 2
<b>K<sub>ATP</sub></b>	ATP-dependent K <sup>+</sup> channel	<b>PDE5</b>	phosphodiesterase 5
<b>K<sub>Ca</sub></b>	Ca <sup>2+</sup> -activated K <sup>+</sup> channel	<b>PDGF</b>	platelet-derived growth factor
<b>K<sub>ir</sub></b>	inwardly rectifying K <sup>+</sup> channel	<b>PDGF-<math>\beta</math></b>	platelet-derived growth factor subunit B
<b>K<sub>v</sub></b>	voltage-dependent K <sup>+</sup> channel	<b>PE</b>	phycoerythrin
<b>LA</b>	left atrium	<b>PECAM</b>	platelet endothelial cell adhesion molecule
<b>LCN</b>	local circuit neuron	<b>PG</b>	prostaglandin
<b>LD</b>	lamina densa	<b>PGI<sub>2</sub></b>	prostacyclin
<b>LDH</b>	lactic dehydrogenase	<b>P<sub>i</sub></b>	internal pressure
<b>LHA</b>	lateral hypothalamic nucleus	<b>PI<sub>3</sub></b>	phosphatidyl inositol-3
<b>L-NMMA</b>	L-N <sup>G</sup> -monomethylarginine	<b>P<sub>i</sub>O<sub>2</sub></b>	inspired partial pressure of O <sub>2</sub>
<b>loxP</b>	locus of X-over P1	<b>PIP<sub>2</sub></b>	phosphatidyl inositol bisphosphate
<b>LPBN</b>	lateral parabrachial nucleus	<b>PKA</b>	protein kinase A
<b>LQTS</b>	long-QT syndrome	<b>PKB</b>	protein kinase B
<b>LR</b>	lamina rara	<b>PKC</b>	protein kinase C
<b>LV</b>	left ventricle	<b>PLA<sub>2</sub></b>	phospholipase A <sub>2</sub>
<b>LVEDP</b>	left ventricular end-diastolic pressure	<b>PLB</b>	phospholamban
<b>MAP</b>	mean arterial pressure	<b>PLC</b>	phospholipase C
<b>MCA</b>	middle cerebral artery	<b>P<sub>o</sub></b>	external pressure
<b>MCP</b>	mean circulatory pressure	<b>PP1</b>	protein phosphatase 1
<b>MHC</b>	myosin heavy chain	<b>PP2</b>	protein phosphatase 2
<b>MLC</b>	myosin light chain	<b>PROX1</b>	prospero homeobox protein 1
<b>MLCK</b>	myosin light chain kinase	<b>PRU</b>	peripheral resistance unit
<b>MPI</b>	myocardial perfusion imaging	<b>P<sub>v</sub></b>	venous pressure
<b>MRI</b>	magnetic resonance imaging	<b>pVHL</b>	von Hippel–Lindau tumour suppressor
<b>MSA</b>	muscle sympathetic activity	<b>PVN</b>	paraventricular nucleus
<b>MVC</b>	maximal voluntary contraction	<b>RA</b>	right atrium
<b>NA</b>	nucleus ambiguus	<b>Rac1</b>	Ras-related C3 botulinum toxin substrate 1
		<b>Rap1</b>	Ras-related protein Rap-1A
		<b>RCT</b>	randomized controlled trial



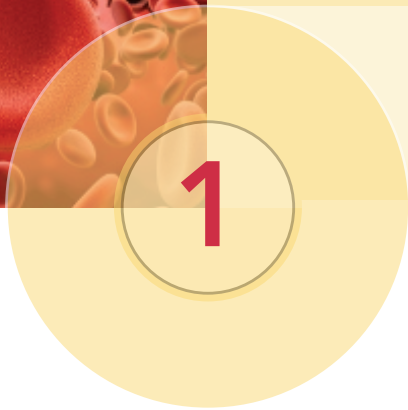
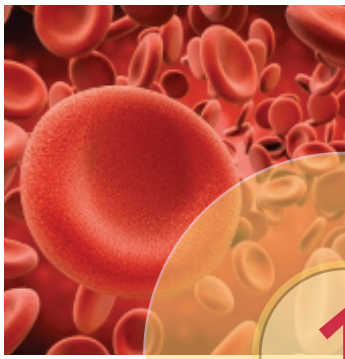
<b>REM</b>	rapid eye movement	<b>TGF-<math>\beta</math></b>	transforming growth factor $\beta$
<b>RhoA</b>	Ras homolog gene family, member	<b>TNF<math>\alpha</math></b>	tumour necrosis factor $\alpha$
<b>RNAi</b>	interference RNA	<b>tPA</b>	tissue plasminogen activator
<b>ROC</b>	receptor-operated channel	<b>TPR</b>	total peripheral resistance
<b>ROCK</b>	Rho-associated protein kinase	<b>TRE</b>	Tet response element
<b>RV</b>	right ventricle	<b>TRP</b>	transient receptor potential
<b>RVEDP</b>	right ventricular end-diastolic pressure	<b>TRPC</b>	transient receptor potential channel
<b>RVLM</b>	rostral ventrolateral medulla	<b>tTA</b>	tetracycline transactivator
<b>RVMM</b>	rostroventral medial medulla	<b>TTX</b>	tetrodotoxin
<b>RyR</b>	ryanodine receptor	<b>TXA<sub>2</sub></b>	thromboxane A <sub>2</sub>
<b>SA</b>	sino-atrial	<b>US</b>	ultrasound
<b>SAC</b>	stretch-activated channel	<b>VCAM-1</b>	vascular cell adhesion molecule 1
<b>SERCA2a</b>	sarcoplasmic/endoplasmic reticulum Ca <sup>2+</sup> ATPase 2a	<b>VDCC</b>	voltage-dependent Ca <sup>2+</sup> channels
<b>SFO</b>	subfornical organ	<b>VE-cadherin</b>	vascular endothelial cadherin
<b>SGP</b>	sialoglycoprotein	<b>VEGF</b>	vascular endothelial growth factor
<b>SHR</b>	spontaneously hypertensive rat	<b>VEGFA</b>	vascular endothelial growth factor A
<b>siRNA</b>	small interfering RNA	<b>VEGFR-2</b>	vascular endothelial growth factor receptor 2
<b>SK<sub>Ca</sub></b>	small-conductance K <sub>Ca</sub>	<b>VEGFR-3</b>	vascular endothelial growth factor receptor 3
<b>SNP</b>	single nucleotide polymorphism	<b>VF</b>	ventricular fibrillation
<b>SOC</b>	store-operated channel	<b>VIP</b>	vasoactive intestinal polypeptide
<b>SON</b>	supraoptic nucleus	<b>VSCC</b>	voltage-sensitive Ca <sup>2+</sup> channel
<b>SP</b>	substance P	<b>VSM</b>	vascular smooth muscle
<b>SPECT</b>	single-photon emission computerized tomography	<b>VT</b>	ventricular tachycardia
<b>SR</b>	sarcoplasmic reticulum	<b>vWF</b>	von Willebrand factor
<b>SSA</b>	skin sympathetic activity	<b>WCT</b>	wide complex tachycardia
<b>SV</b>	stroke volume	<b>XDH</b>	xanthine dehydrogenase
<b>SV40</b>	simian vacuolating virus 40	<b>XO</b>	xanthine oxidase
<b>Tet</b>	tetracycline	<b>YFP</b>	yellow fluorescent protein
		<b>ZO-1</b>	zonula occludens-1



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# Overview of the cardiovascular system

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## LEARNING OBJECTIVES

*After reading this chapter you should be able to:*

- outline the distance limitation of diffusive transport and the roles of diffusion versus convection in oxygen transport (1.1);
- list the differences between the pulmonary and systemic circulations (1.3);
- sketch out how blood pressure (BP), velocity and total cross-sectional area change from the aorta to the microcirculation and to the vena cava (Figure 1.10);
- write down the basic law of flow (1.5) and apply it to work out the main source of vascular resistance;
- sketch the structure of the blood vessel wall (Figure 1.11) and state the roles of the endothelium, elastin, collagen and vascular smooth muscle;
- name five main functional categories of blood vessel and state their roles (1.7);
- define a 'portal circulation' and explain its functional value (1.8).

The heart and blood vessels evolved to transport O<sub>2</sub>, nutrients, waste products and heat around the body rapidly. This is crucial for tissue viability, so the cardiovascular system (CVS) develops at an early stage in the embryo. However, very tiny organisms lack a circulatory system – their O<sub>2</sub> needs are satisfied by diffusion from the environment. Even large animals, such as humans, rely on diffusion for the transport of materials between the bloodstream and cells. Why, then, do we also need a CVS? The answer lies in the distance limitation of diffusive transport.

present, the randomly directed step movements of individual solute molecules result in a net movement down the concentration gradient, i.e. a net diffusive transport (Figure 1.1).

## 1.1 DIFFUSION: ITS VIRTUES AND LIMITATIONS

### Diffusion is brought about by a molecular 'drunkard's walk'

Diffusion is a 'passive' transport process, in the sense that it is driven by the rapid, random thermal motion of molecules, not by metabolic pumps. When a concentration gradient is

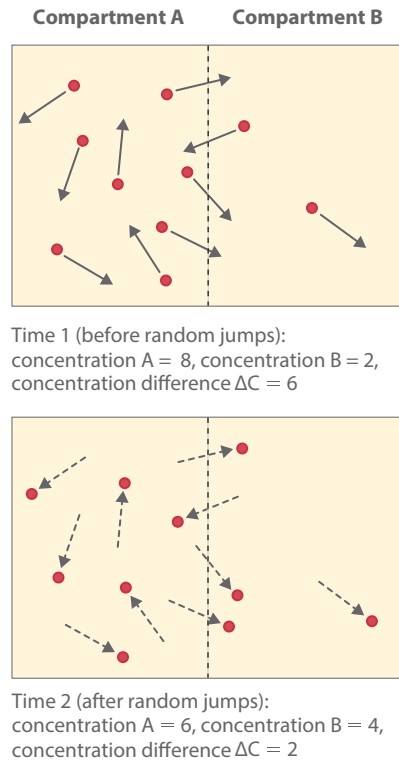
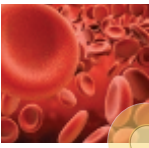
### Distance dramatically slows diffusion

The rate of diffusive transport is important because nutrient delivery must keep up with cellular demand. Fortunately, diffusive transport is very fast over short distances; for example, diffusion from a capillary to tissue cell, a distance of ~10 μm, takes only ~50 ms. Unfortunately, as Einstein showed, the time *t* that randomly jumping particles take to move a distance *x*, in one specific direction, increases as the square of the distance:

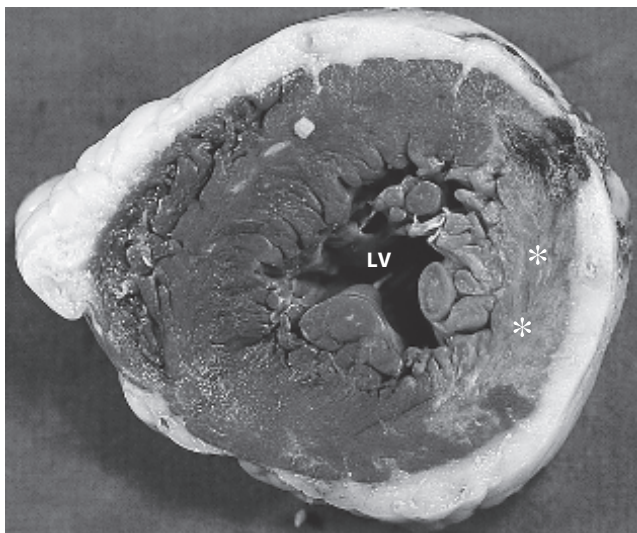
$$t \propto x^2 \quad (1.1)$$

Thus, diffusion is incredibly slow over long distances (Table 1.1). Over 1 cm, which is the thickness of the human left ventricle wall, diffusion would take more than half a





**Figure 1.1** Spontaneous molecular steps in a random direction lead to a net movement of solute molecules (dots) down a concentration gradient. The probability of a randomly directed step from compartment A to B is greater than from B to A because there are more solute molecules in A than B, per unit volume. Note that an individual molecule, such as the top one in B, may move 'uphill', that is, into the more concentrated solution. Net diffusion is thus the result of unequal 'uphill' and 'downhill' fluxes.



**Figure 1.2** Section of the human left ventricle after a coronary thrombosis; the myocardium has been stained for a muscle enzyme. The pale area (marked with two \*) is an 'infarct', an area of muscle damaged or killed by lack of  $O_2$ . The pallor is due to the escape of enzymes from the dying muscle. The infarct was caused by a coronary artery obstruction, which halted the convective delivery of  $O_2$ .  $O_2$  diffusion from blood in the main chamber (LV) is unaffected, yet only a thin rim of adjacent tissue (~1 mm) survived. (Courtesy of the late Professor M Davies, St George's Hospital Medical School, London.)

**Table 1.1** Time taken for a glucose molecule to diffuse specified distance in one direction

Distance (x)	Time (t) <sup>a</sup>	Example <i>in vivo</i>
0.1 $\mu\text{m}$	0.000005 s	Neuromuscular gap
1.0 $\mu\text{m}$	0.0005 s	Capillary wall
10.0 $\mu\text{m}$	0.05 s	Capillary to cell
1 mm	9.26 min	Skin, artery wall
1 cm	15.4 h	Left ventricle wall

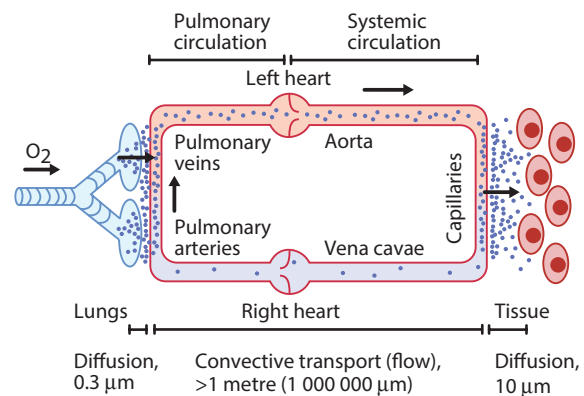
Source: Einstein A. *Investigations on the Theory of the Brownian Movement* (trans. by Fürth R, Cowper AD, 1956). New York: Dover Publications; 1905.

<sup>a</sup> Einstein's equation states  $t = x^2/2D$ , where D is solute diffusion coefficient (glucose,  $0.9 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  at  $37^\circ \text{ C}$ ; oxygen in water,  $3 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ ,  $37^\circ \text{ C}$ ).

day. Sadly, nature often reminds us that Einstein's equation is correct. **Figure 1.2** shows a section through a human heart after a coronary artery thrombus (clot) had blocked off the blood supply to the left ventricle wall. The pale area is cardiac muscle that died from lack of  $O_2$ , even though the adjacent chamber is full of oxygenated blood. The patient died because just a few millimetres reduced the rate of diffusive  $O_2$  transport to a level that was too low to support life.

## Convection provides fast transport over long distances

For distances of  $>0.1 \text{ mm}$ , a faster transport system is clearly needed. The CVS provides this (**Figure 1.3**). The CVS still relies on **diffusion** to transport  $O_2$  across the short distance between gas and blood in the lungs; however, the absorbed  $O_2$  is then washed rapidly along in a stream of pumped fluid, covering a large distance in seconds ( $\sim 3 \text{ cm s}^{-1}$ ). This form of transport is called bulk flow or **convective transport**, and its energy source is the contraction of the heart. Convective transport carries  $O_2$  a metre or more from the lungs to the smallest blood vessels of the human extremities in  $\sim 30 \text{ s}$ , whereas diffusion would take more than 5 years! Nevertheless, diffusion takes over as the dominant transport process for the final  $10\text{--}20 \mu\text{m}$  from blood to cell.



**Figure 1.3** Overview of the human circulation, highlighting the relative roles of diffusion and convection in  $O_2$  transport.