Levick's Introduction to Cardiovascular Physiology

Sixth Edition

Neil Herring and
David J. Paterson

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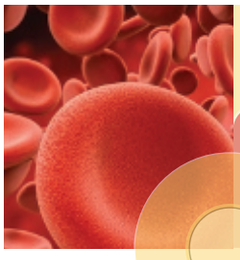
We dedicate this book to our pupils and teachers and the British Heart Foundation
who have supported our research

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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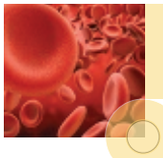

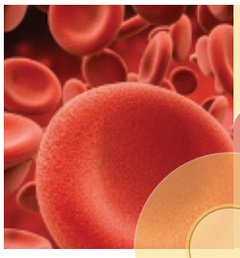

Foreword

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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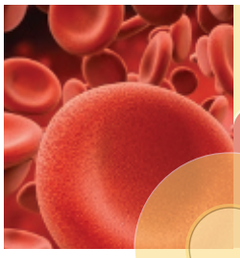

Preface

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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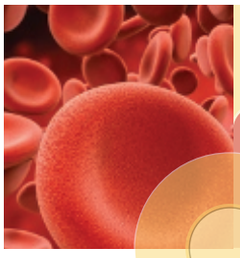
February 2018



A note on active and problem-based learning

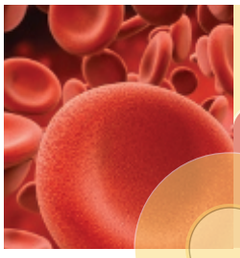
One may read a textbook and gain a primary level of understanding of its subject; however, to master the subject thoroughly *active, 'hands-on' engagement with the subject matter is essential*. In other words, *self-expression* is vital. One may think one knows the subject, but there is nothing like 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.

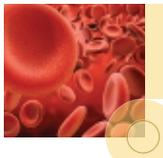
PROBLEM-BASED LEARNING

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.

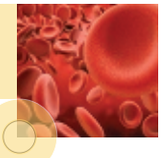


List of abbreviations

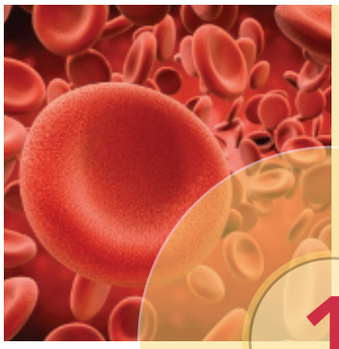
20-HETE	20-hydroxyeicosatetraenoic acid
5HT	5-hydroxytryptamine
AAV	adeno-associated virus
ABP	arterial blood pressure
ABPI	ankle–brachial pressure index
ACE	angiotensin-converting enzyme
ACh	acetylcholine
ADH	antidiuretic hormone
ADP	adenosine diphosphate
AF	atrial fibrillation
AHN	anterior hypothalamic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



GTP	guanosine triphosphate
HCN	hyperpolarization-activated cyclic nucleotide-gated
HCN4	hyperpolarization-activated cyclic nucleotide-gated 4
HDL	high-density lipoprotein
HEK 293	human embryonic kidney cells 293
HF-PEF	heart failure with preserved ejection fraction
HIF-1	hypoxia inducible factor 1
HIP	hydrostatic indifferent point
HIT	high-intensity training
HPV	hypoxic pulmonary vasoconstriction
HR	heart rate
HRE	HIF responsive element
IAP	intra-abdominal pressure
ICA	internal carotid artery
ICC	intercellular cleft
ICD	implantable cardioverter defibrillator
ICP	intracranial pressure
ICS	intercostal space
IK_{Ca}	intermediate-conductance K_{Ca}
IL-1β	interleukin-1β
IML	intermediolateral nucleus
IOI	integrated optical intensity
IP_3	inositol 1,4,5 trisphosphate
iPSC	induced pluripotent stem cell
ITP	intrathoracic pressure
JAM	junctional adhesion molecule
JGA	juxtaglomerular apparatus
K_{ATP}	ATP-dependent K^+ channel
K_{Ca}	Ca^{2+}-activated K^+ channel
K_{ir}	inwardly rectifying K^+ channel
K_v	voltage-dependent K^+ channel
LA	left atrium
LCN	local circuit neuron
LD	lamina densa
LDH	lactic dehydrogenase
LHA	lateral hypothalamic nucleus
L-NMMA	L-N^G-monomethylarginine
loxP	locus of X-over P1
LPBN	lateral parabrachial nucleus
LQTS	long- QT syndrome
LR	lamina rara
LV	left ventricle
LVEDP	left ventricular end-diastolic pressure
MAP	mean arterial pressure
MCA	middle cerebral artery
MCP	mean circulatory pressure
MHC	myosin heavy chain
MLC	myosin light chain
MLCK	myosin light chain kinase
MPI	myocardial perfusion imaging
MRI	magnetic resonance imaging
MSA	muscle sympathetic activity
MVC	maximal voluntary contraction
NA	nucleus ambiguus
NAd	noradrenaline
NAME	nitroarginine methyl ester
NANC	non-adrenergic, non-cholinergic
NET1	norepinephrine transporter 1
NET2	norepinephrine transporter 2
NF	natriuretic factor
NO	nitric oxide
NOAC	novel oral anticoagulant
NOS	nitric oxide synthase
NOS1-AP	nitric oxide synthase adaptor protein
NP	natriuretic peptide
NPY	neuropeptide Y
NTS	nucleus tractus solitarius
NZGH	New Zealand genetically hypertensive (rat)
OVLT	organum vasculosum lamina terminalis
P_A	arterial pressure
$PaCO_2$	partial pressure of CO_2
PAF	platelet-activating factor
PAG	periaqueductal grey
PAH	para-aminohippuric acid
PaO_2	partial pressure of O_2
PAO_2	arterial PaO_2
P_C	capillary pressure
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
P_d	diastolic artery pressure
PDE2	phosphodiesterase 2
PDE5	phosphodiesterase 5
PDGF	platelet-derived growth factor
PDGF-β	platelet-derived growth factor subunit B
PE	phycoerythrin
PECAM	platelet endothelial cell adhesion molecule
PG	prostaglandin
PGI_2	prostacyclin
P_i	internal pressure
PI_3	phosphatidyl inositol-3
P_iO_2	inspired partial pressure of O_2
PIP_2	phosphatidyl inositol bisphosphate
PKA	protein kinase A
PKB	protein kinase B
PKC	protein kinase C
PLA_2	phospholipase A_2
PLB	phospholamban
PLC	phospholipase C
P_o	external pressure
PP1	protein phosphatase 1
PP2	protein phosphatase 2
PROX1	prospero homeobox protein 1
PRU	peripheral resistance unit
P_v	venous pressure
pVHL	von Hippel–Lindau tumour suppressor
PVN	paraventricular nucleus
RA	right atrium
Rac1	Ras-related C3 botulinum toxin substrate 1
Rap1	Ras-related protein Rap-1A
RCT	randomized controlled trial



REM	rapid eye movement
RhoA	Ras homolog gene family, member
RNAi	interference RNA
ROC	receptor-operated channel
ROCK	Rho-associated protein kinase
RV	right ventricle
RVEDP	right ventricular end-diastolic pressure
RVLM	rostral ventrolateral medulla
RVMM	rostroventral medial medulla
RyR	ryanodine receptor
SA	sino-atrial
SAC	stretch-activated channel
SERCA2a	sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a
SFO	subfornical organ
SGP	sialoglycoprotein
SHR	spontaneously hypertensive rat
siRNA	small interfering RNA
SK_{Ca}	small-conductance K_{Ca}
SNP	single nucleotide polymorphism
SOC	store-operated channel
SON	supraoptic nucleus
SP	substance P
SPECT	single-photon emission computerized tomography
SR	sarcoplasmic reticulum
SSA	skin sympathetic activity
SV	stroke volume
SV40	simian vacuolating virus 40
Tet	tetracycline
TGF-β	transforming growth factor β
TNFα	tumour necrosis factor α
tPA	tissue plasminogen activator
TPR	total peripheral resistance
TRE	Tet response element
TRP	transient receptor potential
TRPC	transient receptor potential channel
tTA	tetracycline transactivator
TTX	tetrodotoxin
TXA_2	thromboxane A_2
US	ultrasound
VCAM-1	vascular cell adhesion molecule 1
VDCC	voltage-dependent Ca^{2+} channels
VE-cadherin	vascular endothelial cadherin
VEGF	vascular endothelial growth factor
VEGFA	vascular endothelial growth factor A
VEGFR-2	vascular endothelial growth factor receptor 2
VEGFR-3	vascular endothelial growth factor receptor 3
VF	ventricular fibrillation
VIP	vasoactive intestinal polypeptide
VSCC	voltage-sensitive Ca^{2+} channel
VSM	vascular smooth muscle
VT	ventricular tachycardia
vWF	von Willebrand factor
WCT	wide complex tachycardia
XDH	xanthine dehydrogenase
XO	xanthine oxidase
YFP	yellow fluorescent protein
ZO-1	zonula occludens-1



1 Overview of the cardiovascular system

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_2, 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_2 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.

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 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).

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:

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

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

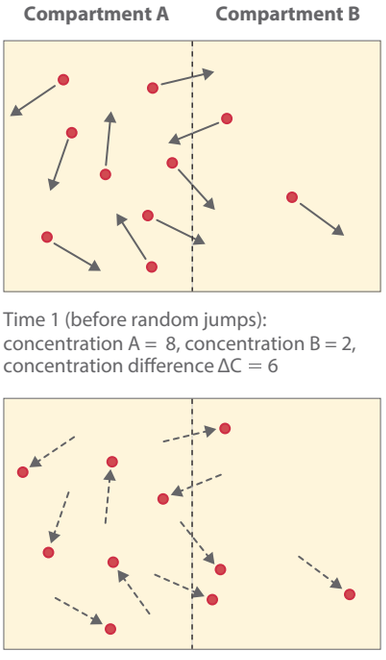


Figure 1.1 Spontaneous molecular steps in a random direction lead to a net movement of solute molecules (dots) down a concentration gradient. The probability of a randomly directed step from compartment A to B is greater than from B to A because there are more solute molecules in A than B, per unit volume. 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.

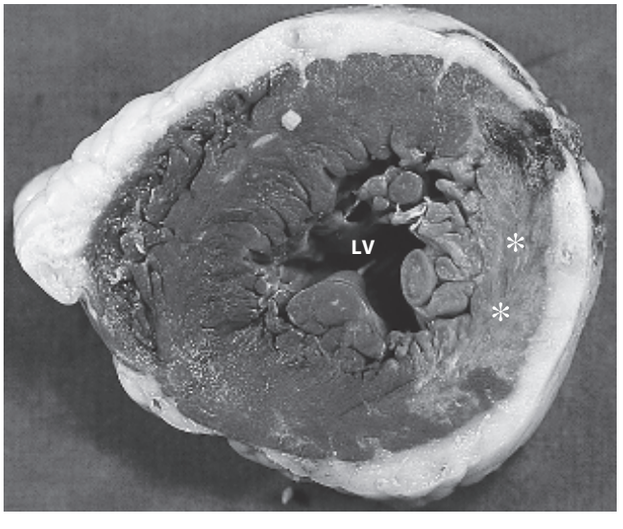


Figure 1.2 Section of the human left ventricle after a coronary thrombosis; the myocardium has been stained for a muscle enzyme. The pale area (marked with two *) is an 'infarct', an area of muscle damaged or killed by lack of O_2. The pallor is due to the escape of enzymes from the dying muscle. The 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)[a]	Example *in vivo*
0.1 µm	0.000005 s	Neuromuscular gap
1.0 µm	0.0005 s	Capillary wall
10.0 µm	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.

[a] Einstein's equation states $t = x^2/2D$, where D is solute diffusion coefficient (glucose, 0.9×10^{-5} cm^2 s^{-1} at 37° C; oxygen in water, 3×10^{-5} cm^2 s^{-1}, 37° 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 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 (~3 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 ~30 s, whereas diffusion would take more than 5 years! Nevertheless, diffusion takes over as the dominant transport process for the final 10–20 µm from blood to cell.

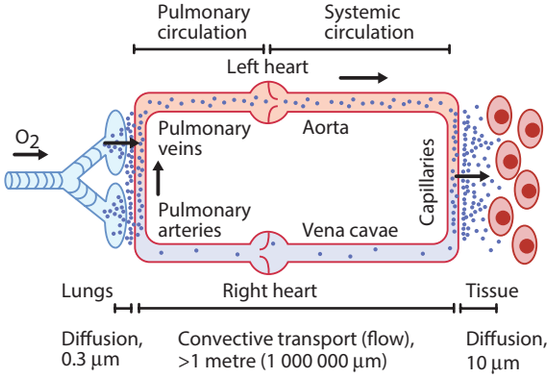


Figure 1.3 Overview of the human circulation, highlighting the relative roles of diffusion and convection in O_2 transport.