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McDonald's Blood Flow in Arteries

THEORETICAL, EXPERIMENTAL
AND CLINICAL PRINCIPLES

SIXTH EDITION

Wilmer W Nichols
Michael F O'Rourke
Charalambos Vlachopoulos

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Sixth edition

Wilmer W Nichols PhD FACC

Division of Cardiovascular Medicine
University of Florida College of Medicine
Gainesville, Florida, USA

Michael F O'Rourke MD DSc FACC FRACP FESC

Cardiovascular Departments
St Vincent's Clinic and Hospital
University of New South Wales
Sydney, NSW, Australia

Charalambos Vlachopoulos MD FESC

1st Cardiology Department
Athens Medical School, Hippokration Hospital
Athens, Greece

With a contribution from

Arnold P Hoeks PhD and **Robert S Reneman** MD PhD

Cardiovascular Research Institute, Maastricht, The Netherlands



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To the memory of friends and colleagues

Donald A McDonald

(Born June 3, 1917; died in Birmingham, AL May 24, 1973)

John R Womersley

(Born June 20, 1907; died in Columbus, OH March 7, 1958)

Michael G Taylor

(Born December 30; 1926; died in Sydney, AU January 10, 2006)

William R Milnor

(Born May 4, 1920; died in Baltimore, MD January 3, 2008)

Raymond P Kelly

(Born December 5, 1956; died in Sydney, AU October 5, 2000)

As an animal Body consists not only of a wonderful texture of solid Parts, but also of large proportion of Fluids, which are continually circulating and flowing, thro' an inimitable Embroidery of Blood-Vessels, and other inconceivably minute Canals: and as the healthy State of an Animal principally consists, in the maintaining of a due *Equilibrium* between those Solids and Fluids; it has ever since the important Discovery of the Circulation of the Blood, been looked upon as a Matter well worth enquiring into, to find the Force and Velocity with which these Fluids are impelled; as a likely means to give a considerable Insight into Animal Oeconomy.

S. Hales

... when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of Science whatever the matter may be.

Kelvin

Science like life feeds on its own decay. New facts burn old rules; then newly developed concepts bind old and new together into a reconciling law.

William James

Die Methode ist Alles

Carl Ludwig

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Foreword by Michael Taylor

It is very pleasant to be invited to provide a few words of introduction to the fifth edition of McDonald's "Blood Flow in Arteries", for it takes me back fifty years, to the first time I met Donald McDonald and John Womersley in January 1955 at St. Bartholomew's hospital in London. Womersley was an applied mathematician at the National Physical Laboratory, and his daughter was a medical student at Barts. She had told him about McDonald's studies on pulsatile arterial blood flow and he became intrigued. By 1955 he and McDonald had been working

together very fruitfully for some time, but no one then would have predicted how far their work would lead. This book first appeared in 1960, and now is going into its fifth edition. Over time its character has evolved, with gradually increasing clinical emphasis, but essentially it remains a tribute to the imagination and foresight of Donald McDonald.

Michael Taylor
Sydney 2004

Foreword by David A. Kass and Myron L. Weisfeldt

With each heart beat, both ventricles eject blood into their respective vascular systems – but do so for only a fraction of the time. The rest of the cycle is allocated to muscle relaxation and refilling of the chambers so the process can start all over again. This fact belies a profound yet often ignored feature of the circulation, namely that, that it is pulsatile. The cyclical nature of flow exiting each ventricle results in pulse pressures that both define the mechanical forces experienced by vascular tissues, and the loads imposed on each ventricle. This hemodynamic behavior is conserved across mammalian species – indeed, the pulse and mean pressure at the base of the brain is remarkably similar between mouse, dog, human, or even giraffe, whose heart has to work a bit extra to provide it. Perhaps not surprisingly, organ physiology has developed to take full advantage of the pulsatile nature of flow and pressure, with vascular signaling that is particularly responsive to vessel stretch and phasic shear stress, and distributed compliances that buffer the pulse as required. As is now well recognized, loss of such buffering capacity and attendant augmentation of the pulse pressure is common in older individuals. Rather than being a ‘normal’ feature of aging, this change is associated with substantial morbidity and mortality. For all the sophisticated molecular biology being applied to identify risks for cardiovascular disease, the simple difference between systolic and diastolic blood pressure is an amazingly potent predictor. Yet for most physicians in medical practice, including those who specialize in cardiovascular disease, we primarily measure and treat means – pressure, flow, resistance – rather than the properties that result in greater pulsatility. While any first-year medical student can define pulse pressure, the properties that give rise to it are traditionally more difficult to measure and can require sophisticated mathematics. As our ability to selectively target arterial properties that lead to excessive pulsatility remain limited, one might reasonably ask, why bother trying?

The answer to this last question and to the many others regarding large artery properties and the pulsatile nature of blood flow are to be found in the newly revised sixth edition of the unparalleled volume, *McDonald's Blood Flow in Arteries*. The authors, all seminal leaders in this field, have updated prior chapters and added several new ones to enhance the discussion in several critical areas. As

before, the book provides a lucid and comprehensive presentation of the history of blood flow and pressure measurements, and the physics and mathematics required to assess pulsatile loading – a.k.a. impedance. They describe newer methodologies that have translated what was once a complex and rather arcane research tool into something more accessible and easily measured in out-patient clinics. In a new chapter on central arterial pressure, methods for its estimation from non-invasively recorded data are explained, and importantly, evidence that such estimation provides better assessment of cardiovascular risk and the benefits of pharmacologic therapy are discussed. Other chapters deal with the impact of pulsatile loading on the heart, blood vessel signaling and biology, and how the normally distensible arterial system in both systemic and pulmonary circulations modulates this pulsatility. There are a number of chapters exploring how vascular pulsatility becomes modified by aging and by disease. A new chapter highlights the impact of common environmental and lifestyle factors as well. Other updated chapters highlight the physiology and pathophysiology of pulmonary and coronary vascular circuits, and in a chapter, this analysis is now extended to cerebral and renal circulations.

The new edition provides an excellent reference for those already engaged in the field, and for those embarking anew as researchers, students, and clinicians. The measurement and understanding of pulsatile circulatory dynamics and its implications to the body are important for clarifying the pathophysiology of many organ diseases, and central for charting the course for better and more appropriate therapies to treat them. This continues to be particularly true in the elderly, a population in which pulsatile features of the circulation are often prominent. The volume is readable, comprehensive, authoritative and remarkably revealing to the casual and expert reader. The subject has always been important, and volumes like this bring to light just why, and will hopefully stimulate new research and disease therapies based upon these insights.

David A. Kass and Myron L. Weisfeldt
Johns Hopkins Medical Institutions
Baltimore, MD, April 25, 2011

Preface

The first edition of *Blood Flow in Arteries* appeared in 1960 as a monograph for the British Physiological Society and introduced a new approach to the study of arterial hemodynamics. It was the product of six years' collaboration between an inventive physiologist, Donald McDonald, a talented applied mathematician, John Womersley, and a young medical graduate, Michael Taylor, at St Bartholomew's Hospital in London – the site of William Harvey's revolutionary work just over 300 years before.

As befits arterial pressure and flow, the first edition concentrated on pulsatile phenomena, and brought to its analysis techniques that were established in engineering science, but had hitherto not been applied comprehensively to a biological system. The major advance was to consider the arterial system as in a 'steady state' of oscillation so that waveforms could be analyzed in the frequency domain – as a series of integral harmonics – and whose relationship with other pulsations could also be considered in the frequency domain. The approach broke completely with the traditional approach of analyzing arterial pulses in the time domain – as a fluctuation over a cardiac cycle between systolic and diastolic values, with peak and nadir of the pressure pulse (systolic and diastolic pressure) considered to have particular physiological and clinical significance.

The new approach considered any pulse waveform as having a mean value, and a fluctuation around this mean, and with the fluctuations capable of being expressed as a series of harmonic components. This new approach stepped further by considering pressure/flow relationships to be near linear, so that the relationships between individual harmonic components of other pulses (of flow at the same site as pressure, or of pressure at another site) could be expressed as a function of frequency. This approach had the advantage of separating pulsatile from steady flow phenomenon and was entirely consistent with the method used then (and now) of relating mean pressure to mean flow for calculation of peripheral resistance. But the new approach, championed by McDonald in his 1960 monograph, was that the arterial system could be considered as a linear system – that any harmonic component of a pressure wave could be related to the same harmonic of another pressure or flow wave recorded at the same time, and to no other harmonic. This was revolutionary (even though linearity was assumed in calculation of resistance from mean pressure and flow). It was, however, soundly based on Womersley's classic mathematical studies on the equations of motion as these applied to blood flow in arteries. Womersley had shown

that the non-linear terms were indeed sufficiently small (in relation to measuring errors) that they could be neglected to a first approximation.

The 1960 monograph ran entirely counter to the prevailing approaches to arterial physiology, particularly as practiced in the United States, but was sufficiently appealing for both Womersley and McDonald to be later attracted to institutions in the USA, and Taylor back to Australia. John Womersley died in Columbus, Ohio as the original monograph was being completed.

Donald McDonald wrote the second edition of *Blood Flow in Arteries* while Professor of Physiology at the University of Alabama in Birmingham. He died when the book was in galley proof stage. The book was completed by his US colleagues Bill Milnor (of Johns Hopkins) and Wilmer Nichols (of the University of Florida). This edition extended the earlier work and introduced some clinical applications.

The third to fifth editions of *Blood Flow in Arteries* were written together by Wilmer Nichols (a pupil of Donald McDonald) and Michael O'Rourke (a pupil of Michael Taylor). At a time when arterial disease was exploding as a clinical problem in developed and developing countries, the book came more and more to consider clinical implications of the original hemodynamic discoveries and to show that the same principles could be expanded and applied to clinical practice – both with regard to the arteries that are affected by disease, and the organs, especially the heart, that are secondarily affected by changes in pressure and flow fluctuations. The authors, both protégés of McDonald, were anxious to retain the attractive features of the original 1960 monograph – emphasis on mechanisms with strong scientific base, embrace of new technology, a focus on practical applications, a comprehensive coordinated style, a disrespect of cant, and a challenge to established authority.

In this sixth edition, we attempt to endorse the same approach to problems of blood flow in arteries as we see them today. The main problems are in the clinical arena and relate to pressure as much as to flow, and to the heart, which generates pulsatile pressure and flow, as well as all organs which require flow so as to live and function normally. Our emphasis remains on arterial pulsations resulting from ventricular ejection, not on the steady component of flow and pressure, and on mechanisms, i.e. on theoretical principles, physiological principles, and clinical principles. This book cannot be a text on arterial disease. It is intended to help those dealing with arterial function, aging, and disease, when they wish to understand underlying principles.

'Principles' and 'reasons' underlie all good practice. 'Evidence' follows. Emphasis on principles may explain why earlier editions of this book have been so popular and so successful in anticipating future developments in clinical practice. As with the first edition, this sixth edition will prove contentious, since it provides a challenge to clinicians and epidemiologists who have seen just one way to measure arterial pressure and cardiac load with the cuff sphygmomanometer. If it succeeds, it will have continued the same approach and traditions, not only of the first edition of 'McDonald', but of Harvey's treatise as well.

This sixth edition appears 50 years after the first. As befits a mature publication which has introduced a new approach to clinical issues related to aging and disease, it is appropriate that the new steps be summarized in the Introduction, then expanded in the text that follows. Scientific advances carry little benefit unless they can be applied. Application requires simplification and approximation. This was done by Einthoven with the electrocardiogram (ECG), by analysis on the basis of an equilateral triangle in the frontal plane of the body. In this sixth edition, which may complete the stewardship of *Blood Flow in Arteries* by the first two authors, we expand

McDonald's concept of linearity into 'Fifteen Commandments' (or general principles) which may guide further advance in the clinical arena. These are summarized in Chapter 1.

We cannot adequately thank those we should in extending the work of illustrious pioneers. We have encountered the same frustrations and setbacks as have they, yet have received generous support from colleagues around the world. We are especially grateful to Arnold Hoeks and Robert Reneman from the Cardiovascular Research Institute, Maastricht, The Netherlands for their assistance with Chapter 5 (Endothelial function) and their contribution of Chapter 8 (Ultrasound). Our younger colleagues are extending this work and have our admiration and respect, particularly Ray Kelly, whose premature death robbed this field and this book of a worthy heir. Above all we thank our dear wives, Arlene, Margaret, and Antonia, who have contributed more than anyone could know.

Wilmer W Nichols
Michael F O'Rourke
Charalambos Vlachopoulos

List of Abbreviations

AASI	arterial stiffness index	EDRF	endothelium-derived relaxing factor
ABI	ankle-brachial index	EECP	enhanced external counterpulsation
AC	alternating current	EMF	electromagnetic flowmeter
ACCT	Anglo-Cardiff Collaborative Trial	eNOS	enzyme nitric oxide synthase
ACE	angiotensin-converting enzyme	EPC	endothelial progenitor cells
ACEI	angiotensin-converting enzyme inhibitor	ESPVR	end-systolic pressure-volume relationship
ACEI	angiotensin-converting enzyme inhibitors	ESRD	end-stage renal disease
ACEI	angiotensin-converting enzymes inhibitors	FAI	flow augmentation index
ACh	acetylcholine	FF	form factor
AGE	advanced glycation end product	FFR	fractional flow reserve
AGE	advanced glycosylation end-products	FMD	Flow-mediated vasodilation
AHA	American Heart Association	FMD	flow-mediated dilation
AIx	augmentation index	HRT	hormone replacement therapy
ARB	angiotensin receptor blocker	iCFR	Invasive CFR
ARB	angiotensin receptor blockers	ICG	impedance cardiography
ARB	angiotensin receptor type 1 blocker	IMT	intima-media thickness
ARIC	Atherosclerosis Risk in Communities	IMT	intima-medial thickness
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial	ISH	International Society of Hypertension
BA	brachial artery	ISH	isolated systolic hypertension
BHS	Bogalusa Heart Study	IVUS	intravascular ultrasonic
BLSA	Baltimore Longitudinal Study of Aging	IVUS	intravascular ultrasound
BP	blood pressure	IVUS	invasive intravascular ultrasound
CAC	coronary artery calcium	L-NMMA	L-monomethyl arginine
CAD	coronary artery disease	LBBB	left ventricular bundle branch block
CAFE	Conduit Artery Function Evaluation	LDA	laser Doppler anemometry
CC	compliance coefficient	LDF	laser Doppler flowmetry
CCA	common carotid artery	LDL	low-density lipoprotein
CCB	calcium channel blocker	LV	left ventricular
CCB	calcium channel blockers	MAP	mean aortic pressure
CCTA	coronary CT angiography	MCP	monocyte chemoattractant protein
CDC	Center for Disease Control	MESA	Multi-Ethnic Study of Atherosclerosis
CFA	common femoral artery	MI	myocardial infarction
CFR	coronary flow reserve	MMP	matrix metalloproteinase
cGMP	cyclic guanosine monophosphate	MP	microparticles
CHD	coronary heart disease	MRI	magnetic resonance imaging
CO	cardiac output	NO	nitric oxide
CPTe	chronic pulmonary thromboembolism	NTG	nitroglycerin
CRP	C-reactive protein	NYHA	New York Heart Association
CT	computed tomography	OCT	optical coherence tomography
CUPS	Chennai Urban Population Study	P-V	pressure-volume
CV	cardiovascular	PA	pulmonary arterial
CVD	cardiovascular disease	PAD	peripheral arterial disease
CW	continuous wave	PAT	pulse amplitude tonometry
DC	direct current	PDA	patent ductus arteriosus
DC	distensibility coefficient	PDE5	phosphodiesterase 5
DHEA	dehydroepiandrosterone	PDE5	phosphodiesterase type 5
DPTI	diastolic pressure-time index	PDE5	phosphodiesterase-5
ECG	echocardiogram	PET	positron emission tomography
ECG	electrocardiogram	PI	pulsatility index
EDRF	endothelial-derived relaxing factor	PP	pulse pressure

PPH	primary pulmonary hypertension	SHM	simple harmonic motion
PRAM	pressure recording analytical method	SIH	secondary intracranial hypertension
PRF	pulse repetition frequency	SMC	smooth muscle cells
PRU	peripheral resistance unit	SNR	signal-to-noise ratio
PWA	pulse waveform analysis	SPTI	systolic pressure–time index
PWV	pulse wave velocity	SRES	shear rate estimating system
QCA	quantitative coronary angiography	SV	stroke volume
RBC	red blood cell	TEE	transesophageal echocardiography
REASON	pREterax in regression of Arterial Stiffness in a contrOLled double-bliNd	TGF- β	transforming growth factor- β
RF	radiofrequency	TTI	tension–time index
RR	relative risk	US	ultrasound
rtPA	recombinant tissue plasminogen activator	VSD	ventricular septal defect
SAC	systemic arterial bed	WBV	whole blood viscosity
SFA	superficial femoral artery	WSR	wall shear rate
SHEP	Systolic Hypertension in the Elderly Project	WSS	wall shear stress

Introduction

In the beginning	3	Analysis in the frequency and time domains	10
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The most obvious feature of ‘blood flow in arteries’ is that it is pulsatile. Therefore, the field of survey is the character of pulsatile flow and the physical laws governing it. This means that the survey must also comprehend the form of the pressure wave of the pulse, in relation both to the flow wave and to the means by which the pulse wave (of flow, as well as pressure) is propagated over the arterial system.

The ability to measure and interpret variations of pressure and flow in humans depends on an understanding of physiologic principles and is based on a heritage well over 100 years old. Studies of pressure preceded those of flow, since reliable tools were available for pressure measurement 100 years ago, but for flow some 40 years less. Relevant studies of the circulation and of underlying physical principles, however, stretch back over 400 years through Harvey and Newton to Galileo.

Pulsatile pressure is recorded routinely in human cardiovascular diagnostic laboratories, operating rooms, and critical care units in the present generation, and pulsatile flow patterns are now used invasively and non-invasively for the quantification of cardiac and vascular shunts and of valvular and vascular stenoses. These techniques have assumed practical importance in routine cardiologic and vascular diagnostic, investigative, and monitoring procedures.

Earlier editions of this book did not anticipate the full clinical implications and potential application of non-invasive pressure and flow measurements in human studies. In particular, the development of diagnostic ultrasound, applanation tonometry, magnetic resonance imaging (MRI), and computed tomography (CT) were not foreseen. These issues are covered in separate chapters. New to the sixth edition are chapters on central blood pressure, change in pulsatile cerebral and renal blood flow with aging and relevance to syndromes of dementia and kidney function, on physical biomarkers which may

anticipate and help interpret results of forthcoming trials and studies, including Framingham and on lifestyle and the environment.

Earlier editions of this book referred to particular conferences, books and articles that had advanced the field. Such reference is no longer appropriate, since arterial hemodynamics is now a mainstream topic in the literature, including the most august experimental and clinical journals, which deal in cardiovascular function and disease. Implications of central aortic pressure measurement rated discussion in Highlights of the Year in *Journal of the American College of Cardiology* 2009 (DeMaria *et al.*, 2010). An award for the best clinical research paper for 2007 was presented to Peter Lacy for the CAFE study (Williams *et al.*, 2006) by the American Heart Association, while Eugene Braunwald in his keynote address to the American Society of Hypertension’s annual meeting in 2010 stressed the historical studies of Frederick Mahomed on the arterial pressure waveform (Braunwald, 2010). The most eminent general medical journals, such as the *New England Journal of Medicine* and the *Lancet*, however, continue to prefer the older, established approaches to arterial pressure and flow measurement and analysis, with scant reference (except in correspondence) to phenomena such as wave reflection and pressure wave amplification in the arterial tree.

This sixth edition of *Blood Flow in Arteries* seeks to justify its place as a reference in the field of pulsatile flow for those who might wish direction to greater detail elsewhere, but who still want to retain orientation, perspective, and balance in what was, is, and always will be a particularly complex and challenging multidisciplinary area. Our challenge, originally met by McDonald alone in 1960, is to achieve this in a sound but interesting and provocative way.

While our principal interest is in pulsatile flow, we must also deal with pulsatile pressure and diameter as they are related to flow. We will be attempting to redress the

problem pointed out by Jarisch in 1928, and quoted again by Neil in 1983, that:

The development of our knowledge of the circulation has been bedevilled by the fact that the measurement of blood flow is so complicated whereas that of blood pressure is so easy: hence the blood pressure manometer has exerted an almost hypnotic influence, though bodily organs don't need pressure but flow.

Sir James Mackenzie (1917), the father of modern cardiology, was even more scathing in his criticism of those who accepted uncritically the numbers provided by the cuff sphygmomanometer: 'we get now a definite and precise figure which most people imagine to be more scientific'.

There is still preoccupation with the sphygmomanometer in the diagnosis and management of hypertension. At the turn of the century, attention was deflected from diastolic to systolic pressure as the major index of risk in hypertension (Black, 1999; He and Whelton, 1999; Staessen *et al.*, 2000b) and to the importance of large arteries both in determining systolic and pulse pressure and as the target of damage when pressure is high (Laurent *et al.*, 2001b; Boutouyrie *et al.*, 2002). This has led to a new approach to hypertension (O'Rourke, 1976; O'Rourke, 1983a; Nichols *et al.*, 1986b; Ting *et al.*, 1986; Safar, 1987; O'Brien and Staessen, 1999; Safar, 2001; Beevers *et al.*, 2001a, Beevers *et al.*, 2001b, Beevers *et al.*, 2001c), which has been aided by new methods for determining arterial pressure, flow, and diameter non-invasively (Avolio *et al.*, 1988; Kelly *et al.*, 1988a; Kelly *et al.*, 1988b; Kelly *et al.*, 1989a; Kelly *et al.*, 1989b; Kelly *et al.*, 1989c; Kelly *et al.*, 1989d; Kelly *et al.*, 1989e; Kelly *et al.*, 1989f; Pedersen *et al.*, 1993; Pauca *et al.*, 2001; Schofield *et al.*, 2002a; das Chagas de Azevedo *et al.*, 2005; Fesler *et al.*, 2007; Chugh and Bakris, 2007; Giannattasio *et al.*, 2008; Wolak *et al.*, 2008).

The 1990s saw confirmation of the view that systolic blood pressure is of greater importance than diastolic (at least in people over age 60) as a risk factor for cardiovascular disease (Rutan *et al.*, 1989; Folkow and Svanborg, 1993; Franklin and Weber, 1994; Franklin *et al.*, 1997) and saw further development of tonometric and ultrasonic methods for more precise assessment of arterial pressure, flow, and diameter changes (Kelly *et al.*, 1990a; Kelly *et al.*, 1990b; Kelly and Fitchett, 1992; Länne *et al.*, 1992a; Länne *et al.*, 1992b). The landmark SHEP publication (1991) showed that treatment of elevated systolic pressure reduced cardiovascular mortality and morbidity, even in people whose diastolic pressure was normal or low. Tonometric and other methods for recording pressure have been used to identify the boost to pressure in central arteries caused by the early return of wave reflection and have linked such boost to measures of left ventricular hypertrophy and performance. There has been new interest in pulse pressure (systolic minus diastolic) as a marker of arterial stiffness, and a prognostic indicator in

older people (O'Rourke and Frohlich, 1999; Dart and Kingwell, 2001; Safar, 2001; Van Bortel *et al.*, 2001a; Domanski *et al.*, 2002; Franklin *et al.*, 2009; Roman *et al.*, 2009). This issue remains contentious, since older, larger studies have not shown the same superiority of pulse pressure over systolic or diastolic pressure (MacMahon *et al.*, 1990; Prospective Studies Collaboration, 2002; Mosley *et al.*, 2007). An explanation arises when one considers the relative youth of subjects in the trials of entry (when amplification of the pulse is considerable), and the different criteria used for measuring systolic and (particularly) diastolic pressure. As discussed in Chapter 28, this issue can be clarified in the future through measurement of central rather than brachial pressure, and with due consideration of aortic aging change (Benetos *et al.*, 2010; Mitchell *et al.*, 2010; Vlachopoulos *et al.*, 2010a; Vlachopoulos *et al.*, 2010b; Wang *et al.*, 2010; Weber *et al.*, 2010). Interest in pulse pressure is moving on to amplitude and contour of the pressure pulse, and in the central arteries. Ultrasonic methods have been further refined for measurement of arterial caliber (Pedersen *et al.*, 1993; Astrand *et al.*, 2005), arterial caliber change (Sonesson *et al.*, 1994; Reneman *et al.*, 2005), wall thickness (Pearson *et al.*, 1994; Astrand *et al.*, 2005), and flow velocity profiles (Yamamoto *et al.*, 1994; Tortoli *et al.*, 2003), using both invasive and non-invasive approaches (see Chapters 6 and 8) (Dewey, 2009; Hermeling *et al.*, 2009; Joly *et al.*, 2009; Muiesan and Painsi, 2009).

Over the past 25 years, there has been a surge of interest in the vascular endothelium, on substances produced by the endothelium that influence components of the blood within the lumen, and on the tone of smooth muscle in the vessel wall. This subject has commanded the attention of some of the best minds in molecular biology, has been widely covered in the literature, and was the subject of the Nobel Prize Award in 1998 (Moncada *et al.*, 1991; Griffith *et al.*, 1994; Rubanyi, 1996; Cardillo and Panza, 1998). Findings give new insight into such subjects as hemostasis and clot formation (Verhamme and Hoylaerts, 2006), arterial spasm (Kawano and Ogawa, 2005; Yasue *et al.*, 2008; Miwa *et al.*, 2009) and variations of arterial tone (Fields and Makhoul, 1998), and atherogenesis (Dobbaro *et al.*, 2009; Herrera *et al.*, 2010; Napoli and Ignarro, 2009) and cellular proliferation after angioplasty (Torella *et al.*, 2004; Finn *et al.*, 2010; Libby *et al.*, 2010).

Over the past 20 years also, there has been acceptance of plaque disruption as the initial event causing coronary thrombosis and myocardial infarction, and on the value of urgent stenting, and of thrombolysis, used early, for dissolution of the clot and limitation of infarction size, not only in the heart, but in the brain as well (Wang *et al.*, 2006; Ay *et al.*, 2008; Braunwald, 2009; Libby *et al.*, 2009; Sanz *et al.*, 2009a). All this leads on to more precision in the approach to understanding how plaques develop in the first place, the influence of inflammation, and why they disrupt. Attention is directed at disrupting forces

within the arterial wall and shearing stresses on the blood–vascular interface. Attention is also directed at the factors which can limit the benefits of angioplasty and stenting – particularly intimal proliferation with bare metal stents and late thrombosis with drug eluting stents (Htay and Liu, 2005; Mehdizadeh *et al.*, 2009; Nakazawa *et al.*, 2009; Nakazawa *et al.*, 2010).

IN THE BEGINNING ...

The sudden swing from ‘natural philosophy’ into modern science is most vividly characterized in the person of Galileo Galilei (1564–1642). From 1598 to 1610, he was Professor of Mathematics at the University of Padua, Padua, Italy. During this period, William Harvey (1578–1657) was studying medicine there, and although Harvey (1628) never mentioned Galileo in his book *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (Anatomical Essay on the Motion of the Heart and Blood in Animals), it is difficult to believe that he was not influenced by the new quantitative teaching and reasoning in his approach to the problem of the circulation of blood. Others were prepared to accept passage of blood through the lungs into the left atrium and through small systemic blood vessels into the right atrium; it was Harvey who stressed the magnitude of such flow. His challenge to the existing order attracted many detractors, especially in France, and he defended his views with colourful language (Fig. 1.1). Modern cardiovascular physiology and biophysics began with Harvey and *Exercitatio Anatomica de Motu Cordis*. However, Harvey typified another characteristic of many of the later pioneers in this field, i.e. interest, competence, and often prominence in more than one field of endeavor. Perhaps a commitment to science and a catholicity of interest accounted for the unusual multidisciplinary achievements of these men. Galileo achieved prominence as a mathematician and as an astronomer, Harvey as anatomist, physiologist and physician (indeed as personal physician to King Charles I).

Perhaps the greatest mathematician and physicist of all time was Sir Isaac Newton (1642–1727). Newton’s monumental work *Principia Mathematica* contained as an addended proposition the concept of fluid viscosity; this has now become central to the consideration of arterial blood flow, pressure–flow relationships, and vascular resistance. Newton left Cambridge in 1696 to take on and excel at an administrative task as Warden of the Royal Mint in London and to gain office, ultimately as president, of the Royal Society (Manuel, 1968). It was in this capacity that he authorized publication of a book by another Cambridge graduate, the Reverend Stephen Hales (1677–1761), entitled *Haemastaticks* (1733).

Although Galen (130–200 AD) palpated the arterial pulse and classified it in terms of strength, rate, and rhythm, Hales was the first to measure arterial pressure in an animal, to document the response of arterial pressure

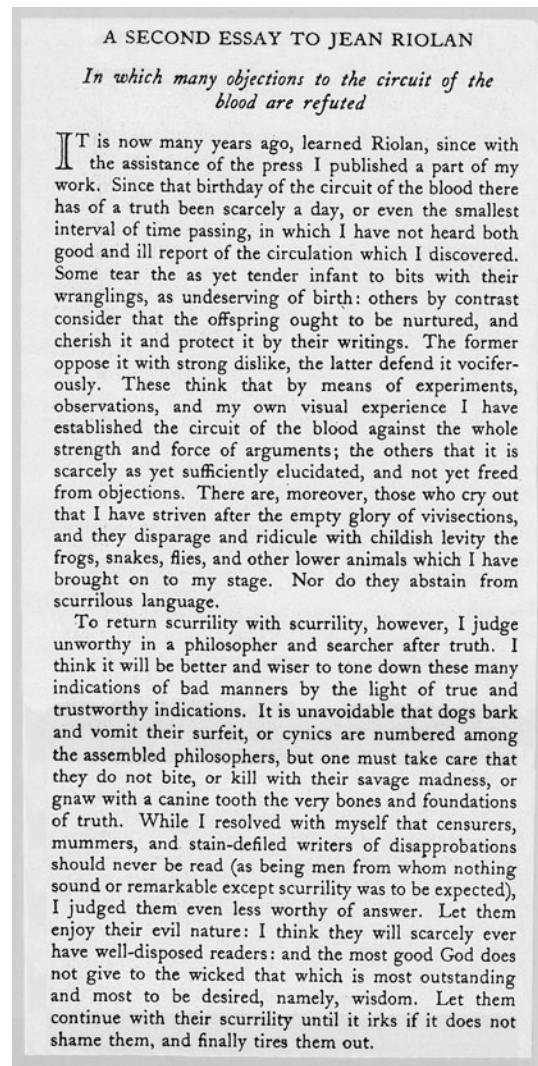


Figure 1.1 Introductory paragraphs of William Harvey's second letter to the anatomist Jean Riolan of Paris. Translated from the original Latin by KJ Franklin of St Bartholomew's Hospital, London

to blood loss, to formulate the concept of peripheral resistance, and to show in an elegantly simple experiment that the greatest resistance to blood flow resides in the tiny blood vessels that are invisible to the naked eye. Hales also likened the arterial system to the inverted, air-filled dome of the contemporary fire engine that smoothed the oscillations due to intermittent pumping so that flow of water through the fire hose nozzle was almost perfectly continuous (Fig. 1.2). Hales saw the arterial system acting as a cushion (or buffer) and the arterioles as resistance to the intermittent pumping of the heart, so that flow through the tissues was virtually devoid of cardiac pulsations. In the German translation of *Haemastaticks*, the fire engine compression chamber was referred to as *Windkessel* – a term which has stuck to the description of the functional cushioning role of the arterial system.

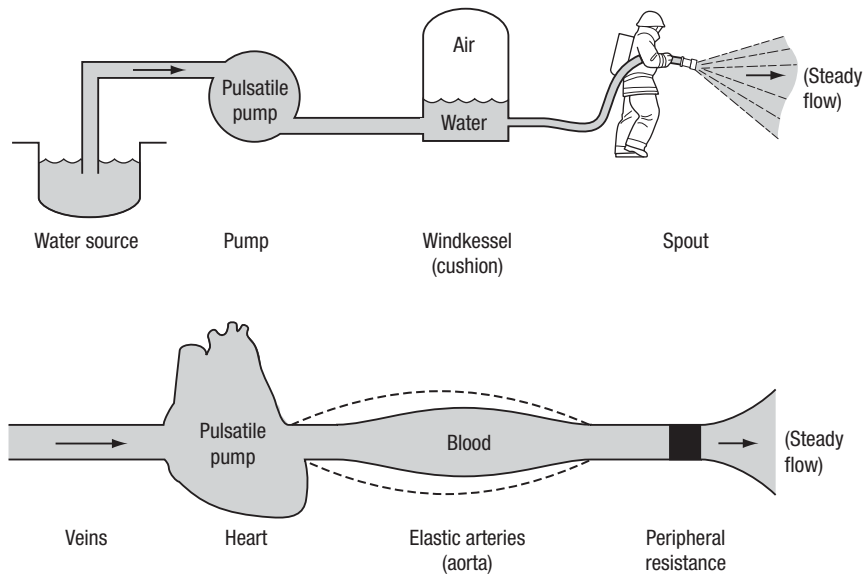


Figure 1.2 The *Windkessel* model of the arterial system. The arterial tree is likened to a medieval fire cart, with distensibility represented by the inverted air-filled chamber, which changes pulsatile flow from the intermittently acting pump, and with peripheral resistance represented by the fire hose nozzle. Reproduced from Westerhof *et al.* (2009)

The eighteenth century was further notable for the great development of the theoretic mathematical treatment of fluid dynamics. While this was based on the work of Newton, it usually dealt with an ‘ideal’ fluid in which Newton’s *defectus lubricatis* or viscosity was ignored. The leader in this field was Leonhart Euler (1707–83), who is described as the most prolific mathematician that ever lived; he established the general equations of fluid motion virtually as they are used today. Euler was a close friend of Daniel Bernoulli (1700–82), who is remembered for his equation describing pressure change with interconversion of potential to kinetic energy.

Daniel Bernoulli was a member of the illustrious Bernoulli family, which included at least three generations of famous and productive mathematicians and physicists (Hopkins, 1991). Daniel, the second son of Jacob’s brother Johann (Fye, 2001), who was a trained physician, learned mathematics from his older brother Nicolaus III. He became Professor of Mathematics in 1725 at St Petersburg, Russia where he did most of the work on his principal opus, *Hydrodynamica*. Life there irked him so greatly that he returned at the first opportunity to Basel, where he became Professor of Anatomy and Botany, and finally of Physics. His mathematical work included calculus, differential equations, probability, the theory of vibrating strings and many other problems in applied mathematics. Daniel Bernoulli has been called the founder of mathematical physics.

The nineteenth century saw further advances in the theory and application of arterial hemodynamics, principally in Germany, England, and France, and again often by young achievers in many disciplines. One of the most prominent was Poiseuille (1799–1869), whose research

in cardiovascular physiology began when he was still a medical student (Hopkins, 1991). Poiseuille was fundamentally a physician with training in physics. His major contribution was to establish the relationship between flow, pressure gradient, and dimensions of a capillary tube; Poiseuille showed experimentally that flow was related to the fourth power of the tube’s internal diameter (1846). Poiseuille’s equation is now expressed as:

$$P_1 - P_2 = \frac{\text{Flow} \times \text{viscosity} \times \text{length} \times 8}{\pi \times (\text{radius})^4}$$

but the precise derivation of this from theoretic principles was attributed to Hagenbach (1860). Poiseuille expressed (viscosity/ π) as a constant. His measurements of relatively low venous pressure in animals (Poiseuille, 1830) suggested to him that a marked drop in pressure must occur somewhere beyond the high pressure that he had measured in arteries down to approximately 2 mm in diameter (Poiseuille, 1828), thus confirming Hales’ contention that the greatest component of peripheral resistance resides in the smallest blood vessels (Fig. 1.3) (Poiseuille, 1828). This (earlier) work explains Poiseuille’s interest in tiny capillary tubes for determining mean pressure–flow relationships.

A man of similar background to Poiseuille as physicist and physician, but who covered an even greater range, was Thomas Young (1773–1829). Young’s scientific exploits are legendary (Hopkins, 1991). His most famous researches in biophysics were concerned with human vision, particularly with the perception of color. The theory that human vision is based on three primary colors – red, green, and violet – is commemorated today as the Young–Helmholtz theory. In fact, his work on light went

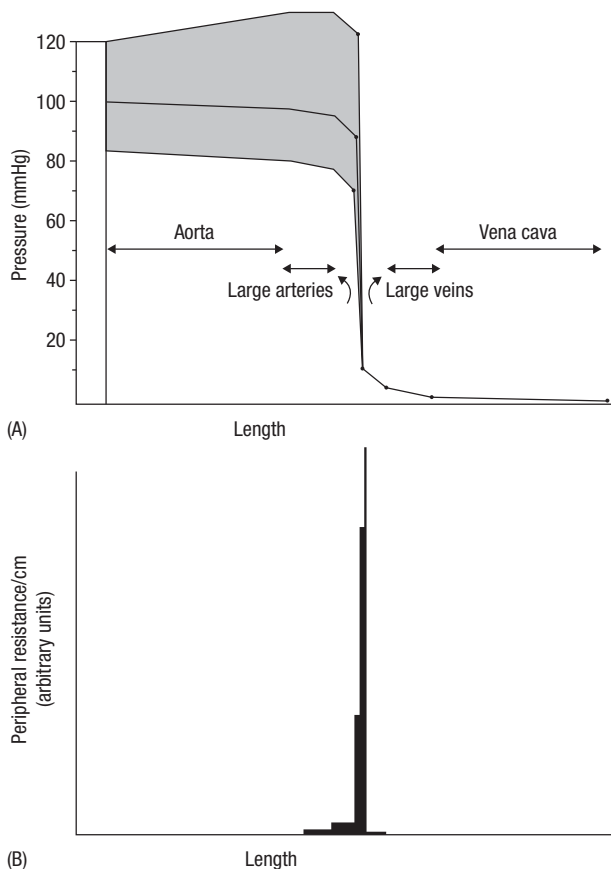


Figure 1.3 (A) Change in pressure between left ventricle and right atrium along the whole vascular pathway. Mean pressure falls precipitously in the arterioles. Pressure wave amplitude is greater in peripheral than in central arteries as a consequence of wave reflection, but falls precipitously in prearteriolar vessels. (B) Change in resistance per unit length along the vascular pathway. Reproduced from O'Rourke (1982b)

much deeper, and that on interference gratings led to the acceptance of the wave nature of light (Williams, 1969). However, the other great body of biophysical work done by Young was into the nature of elasticity, in particular the relationship between the elastic properties of arteries and the velocity of propagation of the arterial pulse (Young, 1808; Young, 1809; Laird, 1980). His work on the nature of elasticity led to the concept of the elastic modulus to which his name is still attached. In determining wave velocity, he derived the formula (given as eqn 3.49) that Bramwell and Hill (1922a) attributed to AV Hill and which other writers (e.g. Bergel and Schultz, 1971) attributed to Otto Frank (1865–1944). This preceded the work of Moens (1878) and of Korteweg (1878) (eqn 3.51) into the relationship between the arterial pulse wave velocity and Young's elastic modulus of the arterial wall. It is finally of interest to add that Thomas Young created an independent reputation in successfully deciphering Egyptian hieroglyphics after the discovery of the Rosetta Stone.

The reference to Egypt creates a link with Fourier (1768–1830), who was one of the band of savants that Napoleon took with him to Egypt and who were stranded there for several years. Fourier's work on the analysis of periodic functions was apparently carried out here and is published in his monograph on heat. Fourier never contributed directly to hemodynamics, but his name occurs so frequently as originator of the Fourier (or harmonic) series that it can hardly be omitted from a historical survey.

The next work of interest in the field of arterial distensibility and wave velocity was the result of collaboration in Germany between the brothers WE and EH Weber (physicist and physician, respectively) and published in a monograph entitled *Wellenlehre* in 1825. This established many of the properties of propagated and reflected waves. This work by the Webers on wave propagation was soon followed by the experimental work of Moens in Leiden, published in his short monograph of 1878. The mathematical analyses of Korteweg and Resal on his data give the equation (written as eqn 3.51) which remains the most useful relationship between pulse wave velocity and arterial properties.

The work of Young, Weber, and other physicians had important clinical implications that were well appreciated at the time. These became more important with the description by Bright (1827) of a relationship between hardening of the arteries, albuminuria, cardiac hypertrophy, and risk of death from stroke and cardiac failure. This work was extended by many, including Marey (1863) and Mahomed (1872) who first described changes in contour of the arterial pressure pulse with age and in hypertension, changes that were forgotten with the introduction of the cuff sphygmomanometer, then rediscovered 100 years later (see Chapter 18) (Braunwald, 2010). Like Poiseuille, Mahomed's research contributions began as a medical student when he developed and described the first quantitative sphygmograph (Mahomed, 1872). Using this, he was the first to detail the natural history of 'essential' hypertension (Mahomed, 1874) and to separate 'essential' from renal hypertension (see Chapter 19 and O'Rourke's (1992), Swales' (1996a), Lewis' (1997), and Cameron and Hicks' (1996) historical tributes to this great pioneer).

The implications of arterial stiffening with respect to cardiac load were, it seems, appreciated at this time, together with the relentless stiffening that occurs in humans with age. Roy (1880) pointed out that 'only in the case of young children do we find that the elasticity of arteries is so perfectly adapted to the requirements of the organism as it is in the case of the lower animals'. The clinical achievements of the later nineteenth century were all the more remarkable when one appreciates that there were no accurate means of measuring arterial blood pressure. The cuff of Riva-Rocci was not introduced until 1896 and the use of Korotkov's sounds not until 1905. Prior to this, high arterial blood pressure was assessed

on the basis of the force required to compress the radial artery and on the amplitude and contour of the arterial pressure pulse. A variety of sphygmographs had been introduced by Marey (1860), Mahomed (1872), Mackenzie (1902), and others, but these could not be calibrated in absolute terms and their dynamic frequency response was poor. Although Torricelli (1608–1647), Galileo's successor as Professor of Mathematics at the Academia in Florence, was the first to use mercury in a glass tube to measure (atmospheric) pressure, Poiseuille (1828) introduced the mercury manometer (U-tube) to measure absolute values of intra-arterial blood pressure. Ludwig (1847) added a float and pointer, enabling pressure to be recorded on a smoked drum. The inertia of such systems was, of course, considerable, so that only mean pressure with slight fluctuations could be obtained. It was known that these small fluctuations occurred simultaneously with cardiac contraction, but their magnitude was too low to represent systolic and diastolic blood pressures. One of Ludwig's pupils, Adolph Fick (Acierno, 2000), was the first to devise a manometer that responded rapidly enough to record systolic and diastolic pressures relatively accurately (1864).

The outstanding difference between the records obtained with Ludwig's mercury manometer and Fick's C-spring recorder was the magnitude of the fluctuations (or pulsations). How large they should be was unknown, and renewed efforts were made to increase the frequency response of the recording system. In 1883, Fick introduced his straight-spring manometer and recorded the first arterial pressure wave that showed a slight hint of a dicrotic notch, although Landois had already demonstrated the presence of a true dicrotic notch in 1874 (Luciani, 1911). He placed a small needle into a dog artery and directed the jet of blood onto the rotating drum of a kymograph. There, clearly displayed, was the dicrotic notch, along with systolic and diastolic pressures. Landois called his record a 'hemautograph'. The development of reliable manometers that could accurately measure pulsatile blood pressure had to await Otto Frank's great work of 1903.

The French physiologist/physician EJ Marey made important contributions not only to non-invasive recordings of arterial pressure waves (Marey, 1863), but also to direct measurements of arterial blood flow. Marey's textbook of 1881 (see Snellen, 1980) includes a complete chapter on the velocity of blood flow in arteries. The technique used was that of a double Pitot tube, which is based on the Bernoulli principle and is used in modern aircraft to measure air speed. (A defective pitot tube is thought to have contributed to the fatal crash of an Air France A330 into the South Atlantic Ocean in 2008.) The Marey tracings look surprisingly like those that we accept as normal today, clearly showing the back flow phase of flow in the carotid and femoral arteries. As with Mahomed's observations, these findings took another 100 years to be rediscovered and accepted (see Chapter 9). Marey's

special interest was in biological motion – of birds in flight and of running horses. His rapid-sequence photographs were the forerunner of modern cinematography (and coronary angiography). As with others previously mentioned, he was a master of many fields. Carl Ludwig appears to have been the first to introduce a continuously recording blood flowmeter. This was an ingenious though awkward device in which blood, flowing through an exteriorized tube, pushed before it a column of oil. As with his pressure recordings, this provided better registration of mean than of pulsatile flow. Adolph Fick is known for the principle enunciated by him that related blood flow through an organ to the arteriovenous concentration gradient of a substance and the amount of the substance taken up or given off by that organ (Fick, 1870). This principle became the standard for measurement of cardiac output in humans following the first human cardiac catheterization by Forssmann (on himself) in 1929 and its popularization by Cournand, Richards, and others in the early 1940s, and the developments which have followed (Mueller and Sanborn, 1995; Ryan, 2002; Braunwald, 2009).

The early twentieth century was completely dominated by Otto Frank and his pupils in Munich. Frank had been highly trained in physics and mathematics and apparently did not turn to physiology until in his late twenties. Frank's first major contribution was to cardiac contraction (in 1895), and it is for this that he is best remembered today. Frank was the first to describe the influence of ventricular dimension on ventricular contraction; this phenomenon, clarified by Starling (Patterson *et al.*, 1914; Starling, 1918), is usually referred to as the Frank–Starling mechanism (Konhilas *et al.*, 2002) or the 'law of the heart' (Katz, 2002). From this early work of Frank sprang the need to produce a manometer that could measure pulsatile blood pressure accurately (Frank, 1903). The manometer that emerged, as with Einthoven's electrocardiogram introduced at the same time (Einthoven, 1903; Fisch, 2000), was based on a very sound physical analysis of the requirements of such an instrument; the analysis remains valid to this day.

Frank passed from cardiac dynamics to manometry, to the measurement of arterial pressure waves, and on to analysis of arterial behavior (Frank, 1905). Frank's penultimate goal was the understanding of arterial properties and arterial function, so that (ultimately) flow could be predicted from pressure change. Beginning with accurate arterial pressure waves, he sought a theoretic basis for arterial function. The framework of his approach was that of manometer theory – that the arterial system behaved like a manometer with a 'lumped' distensible section or *Windkessel* and 'lumped' peripheral resistance. Such analysis ignored wave propagation and wave reflection (McDonald and Taylor, 1959). Frank had the uneasy task of reconciling this theory with the obvious secondary pressure oscillations or diastolic waves that were apparent on his pressure tracings from peripheral arteries. He did

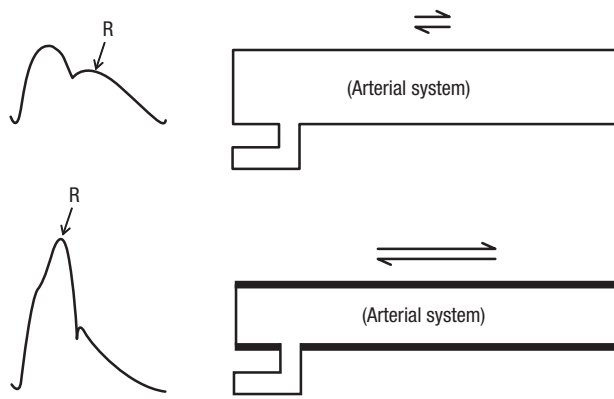


Figure 1.4 Tubular models of the arterial system with the heart (at left) and conduit arteries and lumped peripheral resistance (at right). Coronary arteries are represented by the 'hook'. Pressure waves in the ascending aorta are represented at left. The top model represents the normal youthful arterial tree. The bottom model represents the stiffened arterial tree of an older person with increased aortic pulse wave velocity. Reflection (R) is represented by the diastolic wave in the top case and by the late systolic wave in the bottom case. Reproduced from O'Rourke *et al.* (1987)

so with the awkward compromise of accepting at the same time the infinite wave travel of a *Windkessel* and the finite wave travel of an elastic liquid-filled tube (Fig. 1.4). The solution was more Chinese (related to paradoxical logic) than Germanic (related to Aristotelian logic), more feminine than masculine, utterly uncharacteristic of the man as history portrays him personally. Frank (1899) viewed the arterial pressure pulse as having a *Grundform* or basic pattern upon which was superimposed a *Grundschiwingung* or damped oscillation created by wave travel and reflection generating a type of resonance. A similar approach was later introduced by Cohn and colleagues (Cohn and Finkelstein, 1992; Cohn *et al.*, 1995) and by Davies *et al.* (2007) for calculating the components of arterial compliance. Assuming wave reflection as being from a closed-end reflecting site (as is usually accepted today), Frank proceeded to calculate the length of the *Windkessel* and then went on to estimate flow. The compromise was brilliant. Frank's contributions have been criticized by many (including ourselves) as contradictory and illogical. Viewed from a farther distance in time, and allowing for the primitive state of knowledge at that time and the need to attempt some reconciliation of apparently conflicting observations so that the field might advance, it is clear that one should be far more generous. One's criticisms are more appropriately directed at the unwieldy mathematical edifices that have been created about the initial simple analog model by those followers of Frank who have overlooked the conflicting basic assumptions that were so apparent to him. Such contributions are still seen appearing anew in the literature today (Davies *et al.*, 2007; Cameron, 2009; Manisty *et al.*, 2009). This subject was

well reviewed by Apéria (1940) and by McDonald and Taylor (1959). It was alluded to also by Birkhoff (1960), who, quoting Sir Cyril Hinshelwood, said 'fluid dynamists in the nineteenth century were divided into hydraulic engineers who observed what could not be explained and mathematicians who explained what could not be observed', and added, 'it is my impression that many survivors of both species are still with us'. Some prosper in clinical departments where physical and physiological scrutiny is lacking or dismissed. Good clinical researchers can be 'hoodwinked' (Sharman *et al.*, 2009b).

The First World War destroyed cardiovascular research in Europe. The classic article by Patterson *et al.* (1914) on 'The Law of the Heart' only just made publication, as the sole item in the last issue of the *Journal of Physiology* to be published in five years. Piper was killed in the war. Starling was directed to practical matters of military importance. Frank's work was terminated by the war and never recommenced. His laboratory was destroyed by a bomb shortly after his death at the end of the Second World War. In cardiovascular physiology, the period since the First World War saw the emergence of and ultimate domination by research scientists in the United States. Early pioneers include Katz, Wiggers (a student of Frank), and Hamilton, all of whom wrote influential textbooks and reviews before and after the Second World War. In England, Bramwell and Hill (1922b) described cardiac function in relation to hydraulic load and showed how arterial stiffness (measured as pulse wave velocity (PWV)) was an important component of this load, and how PWV increased in humans with age (Fig. 1.4).

The electromagnetic flowmeter was introduced independently by Wetterer (1937) in Germany (1937) and by Kolin (1936) in the United States. Interference due to the electric potentials created by the heart were overcome, and Deppe and Wetterer (1940) used it successfully on the ascending aorta; its use there and in other arteries in animals became commonplace. Gregg and colleagues (Gregg and Green, 1940; Gregg *et al.*, 1948; Gregg and Fisher, 1963) recorded accurate flow waves in the coronary and other arteries of dogs using this instrument. The period between the world wars had seen little advancement in cardiovascular medicine apart from acceptance of the cuff sphygmomanometer and the electrocardiograph into clinical practice. This period contrasts with that which followed 1944. One can still argue, as did Mackenzie in 1917, that the sphygmomanometer proved a disservice to cardiovascular medicine. While it enabled pressure to be recorded reasonably accurately, quickly, and non-invasively in individual subjects, it concentrated attention on 'the systolic' and 'the diastolic' pressure, inducing an aura of complacency of mind. Clinicians, and indeed researchers, came to consider that systolic and diastolic pressure had some particular biological significance instead of estimating just the highest and the lowest point of a pressure wave in the brachial artery at the time of measurement. Such a view takes no account

of pressure wave amplification between central and peripheral arteries; this renders both systolic and pulse pressure different in different arteries and susceptible to the various influences that alter amplification. The view also encourages the simplistic notion referred to previously, first voiced posthumously in Mackenzie's text but attributable to James Orr, his literary executor, that systolic pressure is a manifestation of cardiac strength and diastolic pressure a manifestation of arteriolar tone (and resistance). This is the basis of the myth that still persists in many quarters that diastolic pressure is the appropriate gauge of elevated arteriolar tone in systemic hypertension (O'Rourke, 1983a; Fisher, 1985; Nichols and Edwards, 2001; Arguedas *et al.*, 2009).

The clinical scene since 1944 has not yet been able to overcome the shackles of restrictive thought that surround concepts of systolic and diastolic pressure, but has exploded in other directions. The introduction of cardiac catheterization by Cournand and Ranges (1941) led to surgical correction of cardiac defects and to the introduction of other invasive and non-invasive techniques into the clinical arena. Intravascular pressure is now recorded routinely not only in the diagnostic laboratory, but in the operating room and critical care area as well. Cardiac output can be recorded by a conventional Fick technique (Acierno, 2000), or by indicator dilution or thermodilution at the same time. Micromanometers have been introduced, permitting the measurement not only of arterial pressure waves and their differentials but also of cardiovascular sound (Murgo and Millar, 1972). Electromagnetic velocity sensors have been miniaturized and mounted on cardiac catheters for the measurement of phasic blood flow velocity (Mills and Shillingford, 1967; Nichols *et al.*, 1980a). Catheter-mounted ultrasonic devices were developed and used for the measurement of flow velocity waveforms (Hartley and Cole, 1974a; Hartley and Cole, 1974b; Bertolet *et al.*, 1996; von Mering *et al.*, 2004; Pepine *et al.*, 2007) and for the visualization of arterial wall structure (Nishimura *et al.*, 1991; Reneman *et al.*, 2006; Nicholls *et al.*, 2008; Bayturan *et al.*, 2009). Ultrasonic techniques have become office procedures for visualizing the chambers of the heart and the blood vessels, and for Doppler non-invasive flow velocity recording. Possibilities for other imaging techniques, such as magnetic resonance imaging and computed tomography, abound and are presently giving new insight into the development of cerebral microvascular disease (Bateman, 2002b; Henry-Feugeas *et al.*, 2005; O'Rourke and Hashimoto, 2007; Lin *et al.*, 2007; Kang *et al.*, 2009). The disease on which they can be used has become not only the most common in the Western world, but correctable to boot (Gibbons *et al.*, 2009; Lauer, 2009; Matter *et al.*, 2009; Wu *et al.*, 2009; Achenbach and Raggi, 2010; Mark *et al.*, 2010).

With the introduction of new methods for measuring phasic blood flow, and with the availability of existing techniques for measuring phasic pressure, a need arose

for more sophisticated analysis of the recorded data. Until 1955, there had been little attempt to do anything other than analyze the waves as they were displayed (i.e. in the time domain). This approach had been explored almost *ad nauseam* for pressure and showed little prospect of giving new information on flow or on the relationship between pressure and flow waves. Physiologists (as well as clinicians) of the time had been content to describe waves in terms of their obvious features, using such descriptive terms as 'foot', 'peak', 'anacrotic wave', and 'dicrotic notch'. This is clearly unsatisfactory from the analytic point of view, however familiar it may be in conveying information of a sort from one person to another. However, the terms used were confusing and descriptions often conflicting (O'Rourke, 1971; O'Rourke, 1982c). Neither the American Heart Association, the American College of Cardiology, nor the European Society of Cardiology have yet been able to provide a consensus document on description and terminology of that most fundamental of all signs, the arterial pulse! Yet methods of description and of analysis have been available and routinely used in the physical sciences. These, of course, utilize the fundamental language of science – mathematics. This subject was addressed by DA McDonald with the mathematician John Womersley in a series of papers published in 1955 and afterwards (McDonald, 1955; leading up to the review by McDonald and Taylor (1959) and the first edition of this book in 1960. The most fundamental and important advance was the demonstration that the arterial system could be viewed as being in a steady state of oscillation, so could validly be analyzed in the frequency domain (Fig. 1.5).

THE ARTERIAL SYSTEM IN STEADY-STATE OSCILLATION

In an attempt to apply mathematical techniques to the circulation, it is obvious that one must be able to describe the phenomena studied in such a way that numerical values can be attached to them. In terms of physical and mathematical practice, a wave is regarded either as an isolated phenomenon or as a repetitive one. That is, it is a transient or it is a periodic oscillation. As the mathematical description of a periodic oscillation is simpler than that of a transient one, it was considered reasonable to suppose that it was the preferred approach, provided that it was valid. Regularity of the heart beat is one of its most characteristic features, and in terms of the length of an individual pulse this regularity is normally maintained for a very long period of time. This is indeed a condition of steady-state oscillation. In these circumstances, any wave that is repeated regularly can be represented by a Fourier series; that is, the wave shape can be described as the sum of a set of sinusoidal waves whose frequencies are

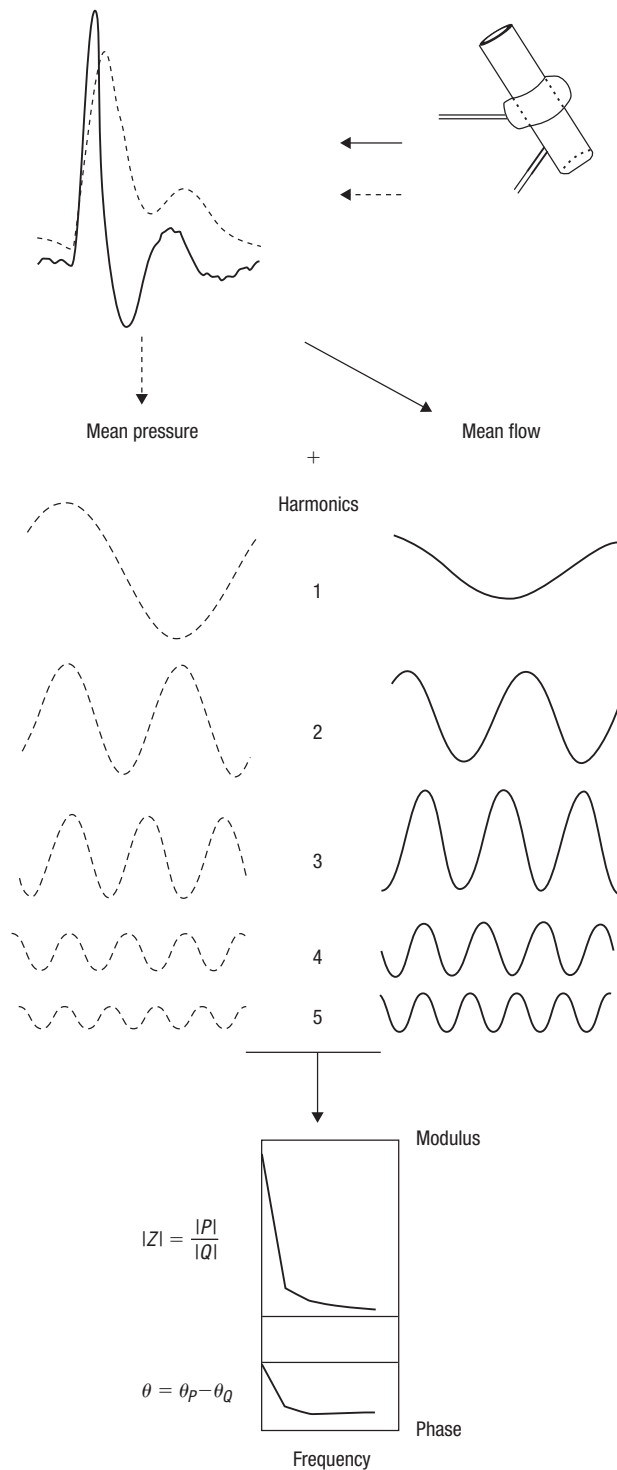


Figure 1.5 Use of Fourier analysis to determine arterial input impedance. Pressure (dotted line) and flow (solid line) measured in a peripheral artery are decomposed into mean values and a series of harmonic (sine) waves at multiples of heart rate frequency. Only the first to fifth are shown. Impedance modulus (top line of lower panel) is the modulus of pressure (P) divided by modulus of flow (Q) at the different frequencies, and phase (bottom line of lower panel) is the delay between pressure and flow harmonics. Reproduced from O'Rourke and Taylor (1966)

all integral multiples of the frequency of repetition of the wave.

The Fourier series and the method of performing Fourier analysis are described in Chapter 11. It is familiar to most people in terms of the harmonic analysis of musical sounds, a connection that is emphasized by the use of phrases such as 'harmonic components' or 'over-tones'. It is widely used in the physical sciences of acoustic, electrical, and aeronautical engineering. In physiology, it is generally accepted as a basis for determining the frequency response of manometers and for recording arterial pressure pulses (see Chapter 6). It is, therefore, logical to extend its use to the flow pulse and the physical relation between pulsatile pressure and flow. It has the advantage of dealing with simple harmonic motion, which, mathematically, is the most tractable form of oscillatory motion, the compound synthesized curve or wave being the simple sum of the component harmonic terms. This property of summation of its component terms is one reason for its outstanding usefulness in describing curves. From this is derived the important practical property of the series that the curve described by a certain number of terms is the best approximation possible for that number of terms. Computing further terms will only improve the fit where it is faulty and does not require any alteration in the lower harmonics.

In applying Fourier analysis to the circulation, certain approximations have to be made. In the first place, there are irregularities in the pulse frequency. As it is a requirement for the Fourier series that the system should be in a 'steady state', any alteration in frequency must be allowed to settle down, just as the conditions due to the starting up in a system must have disappeared before a steady state is attained. The rapidity with which a steady state is attained depends largely on the damping in the system which is being driven; in the arterial system of a dog, early evidence suggested that this is attained within 1.0 s and probably within 0.5 s (i.e. once the pulse has been regular for at most two or three beats). Later evidence (O'Rourke and Taylor, 1966) indicated that a steady state could be achieved well within 0.5 s, so that individual waves could be regarded as part of a steady-state oscillation, even though the heart was beating irregularly.

A more complex difficulty with respect to application of Fourier analysis arises over the question of non-linearity. The circulation is not a linear system, so that, even though a Fourier series may represent a pressure pulse or a flow pulse, one cannot, strictly speaking, say that one harmonic term of pressure is related exclusively to the corresponding harmonic term of flow. The harmonic components must interact with each other. This non-linear effect was calculated by Womersley (1957b) with respect to the motion of blood and found to be small enough to be regarded as negligible to a first-order approximation. Later experimental work has confirmed Womersley's predictions again and again (Dick *et al.*, 1968; Nichols *et al.*, 1977a; Noble, 1979b; O'Rourke,

1982a; O'Rourke, 1982b; Milnor, 1989). This issue is no longer a subject of contention, though it could re-emerge as more accurate measuring and analytical techniques are introduced.

The physical reality of the Fourier representation of impulses having complex shape has often been debated. The apparent artificiality of the statement that the only frequencies represented are integral multiples of the fundamental frequency suggests to the skeptic that this is merely a mathematic device. Yet it can easily be seen that if frequencies other than integral multiples were present, they would not repeat at the fundamental interval, so successive waves would not be of the same form, which denies the condition for applying the analysis. Put another way, this means that the cyclical period to be analyzed must be one in which the whole pattern is exactly repeated.

Further discussion on Fourier analysis, frequency spectrum analysis (Taylor, 1966a; Taylor, 1966b; Taylor, 1966c; Taylor, 1966d), and other analyses of wave contour is presented in Chapter 11. Womersley, McDonald, and Taylor established the validity and suitability of applying Fourier analysis to circulatory phenomena even if they were not the first to propose its use (Apéria, 1940; Porjé, 1946; Randall, 1958; McDonald and Taylor, 1959). This approach has been utilized by many over the last 50 years and forms the basis for the work presented in this sixth edition of *Blood Flow in Arteries*, as it did in the first edition.

ANALYSIS IN THE FREQUENCY AND TIME DOMAINS

The concept of the arterial system as being in steady-state oscillation is stressed here because it is foreign to most physiologists and physicians, and because it has been so helpful to us in studies of the arterial system. It has, however, led to the more general concept of frequency spectrum analysis (Taylor, 1965), which, while it does in theory describe the pulse (or better still a series of pulses) as a transient, expresses results in the frequency domain just as does Fourier analysis, while having the additional advantage of covering the whole frequency range between the individual harmonic frequencies of a single pulse. The full potential is realized when applied to data obtained with the heart beating irregularly, as with random electrical stimuli applied to the heart or when the heart rhythm has converted to atrial fibrillation (Taylor, 1966d). Frequency spectrum analysis and other analytical techniques, including the method of characteristics and controversial use of wave intensity analysis, are described more fully in Chapter 11.

It goes without saying that the results of one method of analysis must be reconcilable with the results of another method when applied to the same data. It should be possible to reach the same conclusions with any analytic

method. This was a problem at the time that the first edition of this book was published in 1960, when the field of arterial hemodynamics was polarized into those who could only see the pulse as a transient (see Hamilton, 1962; Spencer and Denison, 1963), and those like McDonald who could only see the pulse as a series of harmonics. It is possible to draw these two approaches together and link them with others (see Avolio *et al.*, 2009a; O'Rourke, 2009a; and other papers in a special issue of *Medical, Biological, Engineering and Computing*).

In a book such as this, emphasis must be given to details, theoretic and experimental, of blood flow and pressure–flow relationships in different segments of the arterial tree, but the overall perspective of the circulation and its purpose must be retained. Described in its simplest form, the circulation consists of a pump, the heart, which forces blood periodically and rhythmically into a branching system of elastic tubes. The pulsations so generated travel centrifugally and are partially reflected at points of discontinuity (or change in impedance) to travel backwards again (see Chapter 10), while pulsations themselves are normally damped by the time they reach the smallest branches, the capillaries, which are in intimate contact with the cells of the tissues. The blood then returns in a more or less steady stream to the right side of the heart with secondary pulsations imposed in veins by skeletal muscular activity and by the heart itself. The circulation is, of course, far more complicated than this, and the arterial system markedly so, with varied geometric patterns of branching, non-uniform elasticity of arteries, non-linear elastic wall properties, and anomalous viscosity of blood in smaller vessels. Solutions to these problems are sought by detailed descriptions of individual parts of the arterial system, using analytic techniques that are foreign to many and often difficult to comprehend. However, once arterial hemodynamics has been dissected into its component parts, one can synthesize the whole from analysis of arterial pressure and flow waves in single arteries; one then finds that the analysis of the whole complex system of the vascular tree proves to be a great deal simpler than a first look suggests. This book has been written in the hope that such a view – of cohesion, of harmony, and of simplicity arising from complexity – can be transmitted to men and women entering the field, with the expectation that young and flexible minds will enlarge and extend the field and provide further clarification. In this spirit, we provide a summary list of what we see has evolved over the 50 years of this book's publication.

APPLICATION TO CLINICAL PROBLEMS

Application requires simplification. On the basis of what is presented throughout this book, and on the presumption that recordings are accurate, we offer the following as present art, and a tentative foundation for future work.