

# Microcirculation of the Heart

Theoretical and Clinical Problems

Edited by

H. Tillmanns W. Kübler H. Zebe

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With 177 Figures

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## Preface

Microcirculation is a rather new field which has been of predominant interest to basic scientists, linking together technical, hemodynamic, and biochemical aspects.

The findings elaborated, however, are not only of theoretical interest, but bear in addition great clinical implications. In clinical cardiology this became quite evident by the use of tracers in order to study myocardial perfusion and by the description of certain clinical entities — such as angina with normal coronary arteries — which are best explained by „disturbed microcirculation”.

With respect to this new developing theoretical and clinical field of cardiac microcirculation it was the aim of the Microcirculation Working Group of the European Society of Cardiology to have a symposium on which all different but clinically relevant aspects of cardiac microcirculation will be covered. This symposium, held in Heidelberg in January 1980, was planned not only for the exchange of concepts and ideas, but was expected to be in addition partially a teaching session; the basic scientists should be directed toward a better understanding of the clinical problems, and the clinicians should learn more about the basic mechanisms regulating substrate and ion exchange in such an important organ as the heart, and furthermore the theoretical limitations of some of the diagnostic and therapeutical procedures should be taught.

Without a lot of help we would never have succeeded in organizing the symposium and editing its results. The program was made by a scientific committee, consisting of Dr. Grant de Lee from Oxford, my co-chairman of the Microcirculation Working Group, Prof. Dr. E. Gerlach, Munich, and Priv.-Doz. Dr. H. Tillmanns as well as Priv.-Doz. Dr. H. Zebe, both from Heidelberg.

Due to the generous financial support of Pharma-Schwarz/Monheim the symposium could take place in a very enjoyable environment. For editing the results we have to thank in addition the Springer Company — especially Dr. Graf-Baumann.

It is hoped that the Heidelberg symposium will be followed by a series of events in order to stimulate a fruitful discussion between clinical and basic scientists interested in different fields of cardiac hemodynamics and metabolism. This was the basic concept of the Heidelberg meeting.

H. Tillmanns W. Kübler H. Zebe

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## Preface

## List of Senior Authors

### Part A. Physiological, Biochemical and Morphological Aspects . . . . . 1

1.	The Arterial Wall — Transport Properties	
	C.G. Caro and M.J. Lever . . . . .	3
	Discussion . . . . .	14
2.	Morphology of the Myocardial Microcirculation	
	W.F.M. Fulton . . . . .	15
	Discussion . . . . .	24
3.	Flow Properties of the Blood. . . . .	26
3.1	Flow Properties of the Blood: Erythrocytes	
	P. Gaetgens. . . . .	26
3.2	Platelets in the Haemostatic Process	
	K.-E. Arfors . . . . .	33
	Discussion . . . . .	33
3.3	Platelet Vessel Wall Interaction in Coronary Artery Disease	
	W. Schneider and H.J. Reimers. . . . .	36
	Discussion . . . . .	38
4.	Coronary Microcirculation . . . . .	39
4.1	Extravascular and Intravascular Resistance . . . . .	39
4.1.1	The Effect of Increases in Cardiac Oxygen Need on Adenosine Formation and Coronary Blood Flow in the Steady State and During the Cardiac Cycle	
	R.M. Berne, I. Thompson, L. Miller, H. Foley, P. Watkinson, and R. Rubio . . . . .	39
4.1.2	Sites of Adenosine Formation in the Heart During Hypoxia	
	J. Schrader. . . . .	49
4.2	Flow in the Terminal Vascular Bed of the Myocardium. . . . .	56
4.2.1	Methods for the Direct Evaluation of the Terminal Vascular Bed of the Ventricular Myocardium	
	M. Steinhausen, H. Tillmanns, H. Thederan, and H. Leinberger. . . . .	56
4.2.2	Pressures and Dimensions in the Terminal Vascular Bed of the Myocardium Determined by an New Free-Motion Technique. . . . .	61

4.2.3	Patterns of Regional Blood Flow Following Reperfusion of Ischemic Myocardium	
	W. Schaper, . . . . .	75
	Discussion . . . . .	84
5.	Changes in Capillary Permeability . . . . .	87
5.1	Changes in Capillary Fine Structure and Function in Acute Myocardial Ischemic Injury	
	R.B. Jennings, R.A. Kloner, C.E. Ganote, H.K. Hawkins, and K.A. Reimer . . . . .	87
	Discussion . . . . .	96
5.2	Microcirculatory Impairment Following Transient Myocardial Ischemia	
	H. Leinberger, H. Tillmanns, S. Hoppe, and W. Kübler . . . . .	98
5.3	Endothelial Diffusion Limitation of Cardiac Substrate Supply and Transport Mechanism Supporting Substrate Exchange	
	H. Kammermeier . . . . .	104
	Discussion . . . . .	108
5.4	Myocardial Capillary Recruitment Studied by Indicator Dilution Curves	
	W.N. Duran . . . . .	109
	Discussion . . . . .	117
6.	Oxygen and Substrate Supply of the Myocardium . . . . .	119
6.1	Oxygen . . . . .	119
6.1.1	Oxygen Supply to the Myocardium	
	D.W. Lübbers . . . . .	119
6.2	Substrates . . . . .	120
6.2.1	Substrate Delivery in Ischemic Myocardium	
	J.R. Neely, T.C. Vary, and A.J. Liedtke . . . . .	120
	Discussion . . . . .	124
6.2.2	Pyruvate Oxidation in the Hemoglobin-Free Perfused Guinea Pig Heart: Effects of Pressure, Work, and Noradrenaline	
	R. Bünger, B. Permanetter, and O. Sommer . . . . .	126
6.2.3	Metabolic Changes in the Ischemic Myocardium. A Tool for Detection and Quantification of Ischemic Areas in the Heart?	
	G.J. van der Vusse, F.W. Prinzen, and R.S. Reneman . . . . .	136
<b>Part B. Clinical Implication of Disturbances in Coronary Microcirculation . . . . . 139</b>		
1.	Pathophysiology . . . . .	141
1.1	Microcirculatory Determinants of Infarct Dimensions	
	S.M. Factor and E.S. Kirk . . . . .	141

1.2	The Three-Dimensional Geometry of Regional Myocardial Ischemia: The Role of the Coronary Microcirculation in Determining Patterns of Injury	
	D.J. Hearse and D.M. Yellon	149
	Discussion	162
2.	Diagnosis—Methods for Evaluating Myocardial Microcirculation in Patients	165
2.1	Tracer Uptake into the Myocardial Cell	165
2.1.1	Control of Thallium Influx in the Myocardium	
	D. McCall, L.J. Zimmer, and A.M. Katz	165
	Discussion	167
2.2	Assessment of Regional Myocardial Perfusion	170
2.2.1	N-13 Ammonia for the Noninvasive Evaluation of Myocardial Blood Flow by Positron Emission Computed Tomography	
	H.R. Schelbert and M.E. Phelps	170
	Discussion	178
2.2.2	Assessment of Regional Coronary Blood Flow by the Pre-cordial Xenon Residue Detection Technique	
	P.R. Lichtlen, H.J. Engel, and H. Hundeshagen	180
	Discussion	193
2.2.3	The Relationship Between Coronary Artery Disease, Myocardial Ischemia and Angina	
	A.P. Selwyn, T. Pratt, K.M. Fox, and R. Steiner	194
2.3	Relative Regional Fractional Myocardial Oxygen Extraction in Dogs Using Oxygen-15-Water and Either Oxygen-15 Deoxy-hemoglobin or Oxygen-15-Oxyhemoglobin	
	J.A. Parker, B. Hoop, G.G. Beller, and T.W. Smith	201
	Discussion	205
2.4	Noninvasive Measurement of Regional Myocardial Glucose Metabolism by Positron Emission Computed Tomography	
	H.R. Schelbert and M.E. Phelps	207
	Discussion	213
2.5	Regional Myocardial Metabolism of Free Fatty Acids	
	K. Vyska, A. Höck, C. Freundlieb, S.N. Reske, A. Schmid, and L.E. Feinendegen	216
	Discussion	
<b>Part C. Clinical Manifestations in Disturbance of Coronary Microcirculation</b>		229
1.	Small Vessel Disease	231
1.1	Morphology	231
1.1.1	Small Vessel Disease, Morphology	
	G. Rahlf	231
	Discussion	251

1.2	Clinical Diagnosis	253
1.1.2	Structural Changes of the Coronary Microcirculation	
	Coarctation of the Aorta	
	H.N. Neufeld, A. Schneeweiss, E. Lehrer, and Y. Liebermann	253
	Discussion	255
1.2.1	Clinical Diagnosis of Small Vessel Disease	
	M. Tauchert, W. Jansen, V. Hombach, B. Niehues, D.W. Behrenbeck, and H.H. Hilger	257
1.2.2	Coronary Hemodynamics in Systemic Arteriopathies	
	B.E. Strauer, H. Schenk, S.B. Bürger, and K.H. Heitlinger	266
	Discussion	279
2.	Syndrome X	283
2.1	Morphology	283
2.1.1	Morphology of Heart Muscle Cells and Myocardial Microcirculation in Patients with Angina Pectoris but Normal Coronary Arteries (Syndrome X)	
	E.G. Weihe, D. Opherk, U. Ryan, G. Mall, H. Zebe, W. Kübler, and W.G. Forssmann	283
2.1.2	Studies in Patients with Abnormal Electrocardiogram of Unknown Etiology	
	H. Kuhn, B. Lösse, and W. Hort	288
2.2	Clinical Diagnosis	296
2.2.1	Reduced Coronary Reserve and Impaired Exercise Left Ventricular Performance in Patients with Syndrome X	
	D. Opherk, H. Zebe, G. Schuler, E.G. Weihe, G. Mall, H.C. Mehmel, B. Gravert, J. Augustin, and W. Kübler	296
	Discussion	300

#### **Part D. Therapeutic Implications** . . . . . 303

1.	Effect of Drugs on Myocardial Microcirculation	305
1.1	The Effect of Coronary Vasodilators on the Microcirculation of the Ventricular Myocardium	
	H. Tillmanns, M. Steinhausen, H. Leinberger, H. Thederan, and W. Kübler	305
	Discussion	311
1.2	Drug-Induced Changes in Myocardial Blood Flow Following Acute Coronary Artery Ligation	
	J.R. Paratt	313
2.	Rheological Aspects	325
2.1	Blood Rheology and Cardiac Microcirculation: Is There a Place for Hemodilution in Coronary Insufficiency?	
	H. Schmid-Schönbein	325
	Discussion	339

2.2	Effects of Hemodilution on Myocardial Blood Flow	
	K. Messmer, L. Chaussy, W.J. Stelter, and W. Stippig	341
	Discussion	345

Subject Index	347
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## Part A

### Physiological, Biochemical and Morphological Aspects



# 1. The Arterial Wall — Transport Properties

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## Introduction

In this symposium concerned with the microcirculation of the heart, it is not, we believe, inappropriate to consider the mass transport of the arterial wall. This is firstly because this transport is thought to play a role in the development of atherosclerosis and, secondly, because it appears that it depends on the wall microcirculation, including the lymphatics.

The emphasis of the present paper is on arterial wall macromolecule transport under steady conditions which can be expected to be obtained *in vivo*. Our initial approach to this complex problem has been to use the relatively inert material serum albumin as the transported species and to work with the rabbit common carotid artery perfused *in situ*. The *in situ* arterial preparation [7, 10] was used, firstly because it has been found possible to cannulate and perfuse arteries *in situ* without damaging the intima [3] or disturbing the adventitia — previous studies have shown that the vasa vasorum contribute to arterial wall mass transport [1, 11] — and secondly because it affords good control of experimental parameters under essentially physiological conditions.

Our findings support the postulate [5, 16, 18] that there is net transport of macromolecules across the arterial wall. They provide, moreover, some understanding of the relevant mechanisms, including the role of the media and of the adventitial circulation. We report in addition some preliminary results we have obtained on the influence of vaso-active materials on the uptake of albumin by the media of segments of this artery when incubated *in vitro*.

## Methods

The rabbit common carotid artery was studied when (1) perfused *in situ* with plasma containing radioactively labelled albumin; (2) perfused as in (1) and simultaneously subjected to gentle irrigation of its outer surface with a solution containing label at the same concentration as in the lumen; and (3) perfused as in (1) after deliberately damaging the intima. Excised segments of the artery were also incubated *in vitro* in labelled plasma. Label uptake was assessed both by determining whole wall radioactivity and by studying the distribution of activity through the thickness of the wall using the technique of sequential frozen sectioning parallel to the intima. The quantity of diffusible native protein in the wall was also determined, and light and transmission electron microscopic studies were undertaken.

$^{125}\text{I}$  albumin was used in the whole wall uptake studies, and in order to achieve the required levels of tissue radioactivity,  $^{131}\text{I}$  albumin was used in the frozen section work. Radioactive iodide was removed from the tracer by dialysis or ultrafiltration. Its concentration was shown to remain low in all the uptake studies.

The perfusion apparatus is illustrated diagrammatically in Fig. 1. Fresh rabbit plasma flowed steadily through the cannulated common carotid artery at physiological levels of luminal hydrostatic pressure and temperature. A slow plasma flow rate ( $4\text{ ml min}^{-1}$ ) was

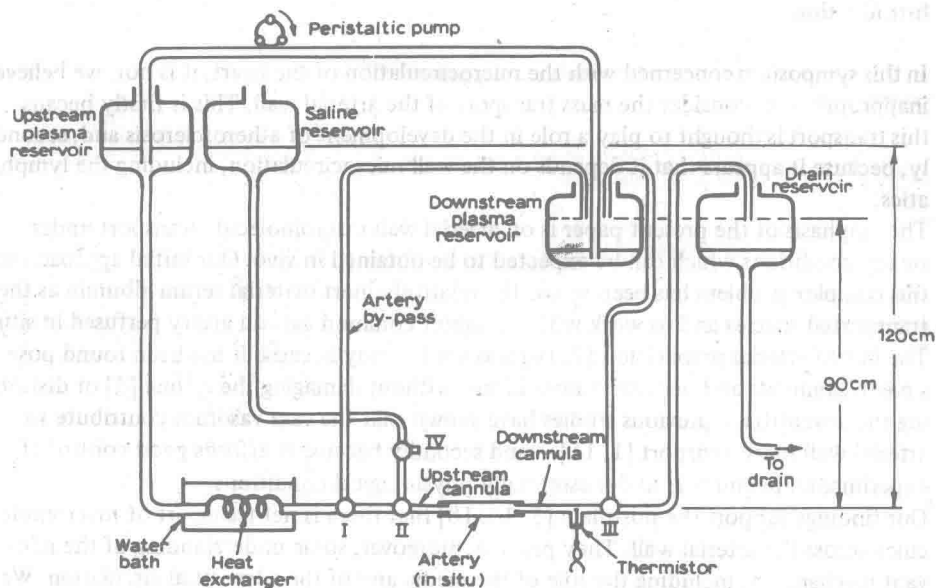


Fig. 1. Perfusion apparatus

used in order to minimize any effect of wall shear stress on label uptake [6, 11]. Pressure pulsations in the artery, due to the pump, were less than 0.01 of the mean luminal pressure.

Cannulation of the artery was achieved with minimal disturbance to it, except over short lengths at its proximal and distal ends and with only slight disturbance of the luminal hydrostatic pressure [9]. Because the animals remained alive throughout the experiments and there was no interference with the branches of the cannulated artery, it was necessary for the luminal pressure to exceed 80-100 cm  $\text{H}_2\text{O}$  in order to prevent blood from the animals' own circulations flowing into the perfusion system. In most experiments, 5-10 ml per hour of labelled plasma flowed from the perfusion apparatus into the animals' circulations.

In eight in situ perfused artery experiments, label at the same concentration as in the lumen, but contained in plasma diluted with an equal volume of Tyrode's solution so as to resemble lymph, was gently run over the outer surface of the vessel throughout the experiment. These studies involved no additional surgery.

In ten experiments, arteries were perfused in situ for periods ranging from 20-90 min, flushed with saline solution and then damaged at their intimal surface by slowly sliding a cannula along the lumen. The cannula was withdrawn to its original location, resecured, and perfusion with the same labelled plasma was resumed for 15-20 min.

At the conclusion of the in situ studies, the arteries were briefly flushed with saline solution at a luminal pressure of 100 cm H<sub>2</sub>O in order to remove label both from the lumen and the vasa vasorum. The animal was then killed with an overdose of anaesthetic, and the artery was quickly excised. End portions of the vessels which might have been damaged and loose adventitia were discarded, and the segments were then blotted and weighed, and their radioactivity was determined.

In the in vitro studies the vessels, after excision, were freed of loose connective tissue, divided into 0.5-cm long segments and stored in plasma for up to 1 h pending their use. In short term (30 s-3 h) studies, the segments were incubated for a predetermined time in labelled plasma, rinsed, blotted, weighed and subjected to determination of their radioactivity. In long term (overnight) studies, they were incubated in labelled plasma in dialysis sacs suspended in buffer at 4°C.

The distribution of radioactivity through the thickness of the artery wall was determined both in in situ perfused and in vitro incubated segments by freezing them and sectioning them parallel to the lumen in a manner similar to that adopted by others [5]. After the tissue was frozen onto prepared cutting blocks, its edges were trimmed to remove any overhang, the projected surface area was determined, and 20 µm sections were cut through the wall. The sections were dried, weighed to check the accuracy of sectioning and to estimate the thickness of the first section, and their radioactivity was determined.

In all the studies, wall uptake was defined as a tissue/plasma activity ratio,  $C_T/C_p$ , that is cpm g<sup>-1</sup> wet tissue/cpm g<sup>-1</sup> plasma (assuming unit density). Plasma label concentration remained constant throughout the in situ and the in vitro studies.

The diffusible native protein in three arteries was determined. The vessels were excised and incubated for 36 h in 0.9% saline solution at 4°C. The extract was then dialysed against 0.9% saline solution at 4°C to remove low molecular weight material, and the protein was determined by Lowry's method. It was related to wet tissue weight.

## Results

Light microscopy, dye exclusion studies with Evans blue added to the perfusing plasma [4], and transmission electron microscopy did not reveal damage in the in situ perfused vessels. Sliding a cannula along the lumen caused endothelial damage (Fig. 2). The whole wall label uptake was determined for 18 arteries perfused in situ for periods ranging from 1 to 90 min. There was no evidence that uptake varied with time. The average value of  $C_T/C_p$  was 0.0067, SEM 0.0009.

For sectioned arteries perfused in situ, the  $C_T/C_p$  value of each section was plotted against scaled distance from the lumen in order to produce an activity profile. There was considerable scatter, particularly affecting the adventitia. The average profile for

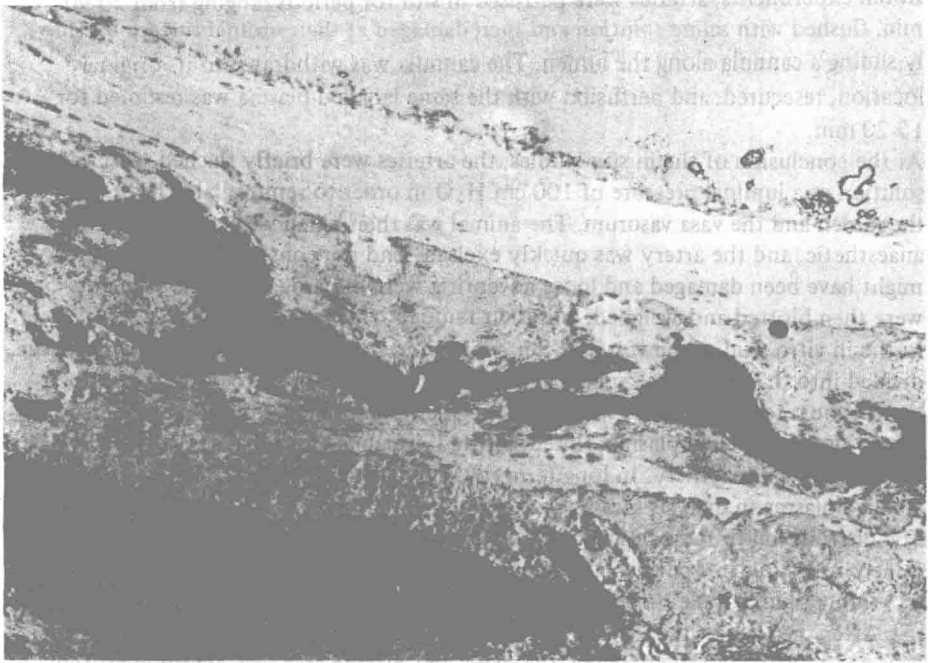


Fig. 2. Transmission electron micrograph of artery after cannula damage to the endothelium

each perfusion time has been plotted in Fig. 3. Mean medial and adventitial  $C_T/C_p$  values were calculated, and these are shown as a function of perfusion time in Fig. 4. The mean medial value increases with time, and an apparently steady value of 0.0095, SEM 0.0013 ( $n = 11$ ) is reached at about 30 min. No firm conclusion can be drawn about the adventitia because of the large scatter.

Mean medial and adventitial values were similarly calculated from the  $C_T/C_p$  profiles obtained from arteries perfused in situ while simultaneously exposed to label at their outer surface. The experiments were of 30 and 60 min duration, and there was no significant difference between either the medial or adventitial values at these two times. The average medial and adventitial values were respectively 0.032, SEM 0.0032 and 0.22, SEM 0.034 (eight arteries).

The average whole wall  $C_T/C_p$  for ten arteries perfused in situ and subjected to intimal damage was 0.42, SEM 0.0096.  $C_T/C_p$  was determined for the whole wall in 20 segments incubated for varying periods of time in labelled plasma in vitro. In addition, the total wall  $C_T/C_p$  was calculated for 57 segments similarly incubated and then subjected to frozen sectioning by summing the section values. The average values at different incubation times are shown in Fig. 5.  $C_T/C_p$  rises with time and reaches an apparently steady value of 0.22 within about 30 min. Whole wall values are also shown for segments incubated in dialysis sacs overnight. The average value is 0.19.

The average  $C_T/C_p$  profiles for segments incubated in vitro for periods ranging from 10 min to 3 h are shown in Fig. 6. The time-dependent behaviour of the mean medial and adventitial values of  $C_T/C_p$  for these vessels is shown in Fig. 7. For the adventitia,