科技资料

Silent Myocardial Ischemia: A Critical Appraisal

International Round Table on Silent Myocardial Ischemia, Tel Aviv, December 3–7, 1989

Silent Myocardial Ischemia: A Critical Appraisal

Editors
Jan J. Kellermann, Tel Hashomer
Eugene Braunwald, Boston, Mass.

80 figures and 49 tables, 1990

KARGER

Basel · München · Paris · London · New York · New Delhi · Bangkok · Singapore · Tokyo · Sydney

Advances in Cardiology

Library of Congress Cataloging-in-Publication Data
International Round Table on Silent Myocardial Ischemia (1989: Tel Aviv, Israel)
Silent myocardial ischemia: a critical appraisal / International Round Table on Silent Myocardial Ischemia, Tel Aviv, December 3–7, 1989; editors, J.J. Kellermann, E. Braunwald.
(Advances in cardiology; vol. 37)
Includes index.
1. Silent myocardial ischemia – Congresses. I. Kellermann, Jan J.
II. Braunwald, Eugene, 1929–. III. Title. IV. Series.
[DNLM: 1. Coronary Disease – congresses. W1 AD53C v. 37 / WG 300 I6133s 1989]
RC681.A25A38 vol. 37
[RC685.S48]
616.1'2 s – dc20
[616.1'23]
ISBN 3–8055–5196–7

Bibliographic Indices
This publication is listed in bibliographic services, including Current Contents® and Index Medicus

Printed in Switzerland by Thür AG Offsetdruck, Pratteln
ISBN 3–8055–5196–7

Preface

This volume of Advances in Cardiology consists of the lectures of the invited faculty of the International Round Table on Silent Myocardial Ischemia which was held under the auspices of the International Society and Federation of Cardiology, The American Heart Association (Council on Clinical Cardiology) and the Israeli Heart Society.

This book is the outcome of a carefully prepared scientific event in which the main goal was to assess critically and discuss silent myocardial ischemia in the broadest sense. As co-chairmen it was our aim that the conference should reflect the concern and doubts of the professional community as to whether or not silent myocardial ischemia should receive attention equal to that of symptomatic ischemic conditions. The contents of this book consists of three round tables of which the first deals with the pathogenesis and diagnosis, the second with pain perception, incidence and prognosis, and the third with clinical implications and management. In addition, the potential for clinical trials was discussed by George Sopko of the National Institutes of Health (USA).

In preparing this conference we were well aware that we were facing a complicated discussion. The reason for this is that there is an ever increasing number of articles and books published on this topic and one may easily receive the false impression that nothing remains to be said about the various aspects of silent ischemic conditions. In perusing the present literature it was obvious that there still exists a large number of question marks posed by experienced researchers who are particularly interested in this field, but also many clinicians have asked the question whether silent myocardial ischemia is merely a passing fancy. Others feel that there is still considerable confusion and that therefore there is a need to postulate, in an

authoritative manner, what can be scientifically documented and what should be considered as vague and problematic. We hope that our book will clarify some of the problems concerning this condition and hopefully answer some other questions which have been raised and not answered so far. We have tried to reflect the various exchanges of opinions and analyses of the subjects deliberated during the conference, which provided an ample time for an extensive discussion.

We hope that with the assistance of a distinguished and internationally renowned faculty we have succeeded, at least in part, to fulfil our objectives and the expectations we set ourselves in this conference. We have also learned that more research is needed to improve diagnostic validities and to reply to pertinent questions established as to the therapeutic management to be applied in patients with silent myocardial ischemia. We should like to pay tribute to our faculty who not only contributed actively, but also participated constructively in a profound and broad discussion.

We would like to take this opportunity to express our gratitude and appreciation to Bayer AG, Leverkusen, for the publication grant extended to us which enables a wide distribution of this book.

Last, but not least, we would like to thank the main sponsors of the meeting, Bayer AG, Hewlett Packard SA, Merck, Sharp & Dohme, Schwarz Pharma AG. Without their generous support this conference would not have become a reality.

Jan J. Kellermann
Eugene Braunwald

Contents

Pain Perception – Incidence – Prognosis

Clinical Implications – Management

Introduction

Kellermann JJ, Braunwald E (eds): Silent Myocardial Ischemia: A Critical Appraisal. Adv Cardiol. Basel, Karger, 1990, vol 37, pp 1–6

Asymptomatic Ischemia: Resolved and Unresolved Issues

Eugene Braunwald

Harvard Medical School, Department of Medicine,
Brigham and Women's Hospital, Boston, Mass., USA

During the past decade it has been appreciated increasingly that many patients with serious coronary artery disease never have symptoms and that in an even larger number the majority of ischemic episodes, including episodes of acute myocardial infarction, are asymptomatic. Asymptomatic (silent) ischemia has appropriately attracted the attention of clinicians, basic scientists, and epidemiologists. The purpose of this introduction is to summarize some of the most important information on asymptomatic ischemia about which there is general agreement (resolved issues) and to identify some of the most important gaps of information (unresolved issues).

Sixteen major resolved issues are shown in table 1. These include the enormous incidence and prevalence of asymptomatic ischemia, the broad array of clinical circumstances in which it occurs, including stable and unstable angina, myocardial infarction, occult coronary artery disease and sudden death, as well as the factors which precipitate it, such as mental stress and cigarette smoking. It is agreed that asymptomatic ischemia may be detected by a variety of techniques, including exercise electrocardiography, ambulatory (Holter) electrocardiography, myocardial perfusion scintigraphy, radionuclide ventriculography and positron emission tomography. Ambulatory electrocardiography is less sensitive than exercise testing in the detections of asymptomatic ischemia, but it is extremely useful in at least two groups of patients: (1) those who cannot exercise, and (2) those with Prinzmetal's angina whose episodes of ischemia, some of which are silent, usually occur at rest. Ambulatory electrocardiography also is *not* an ideal technique for screening apparently healthy persons for asymptomatic

Table 1. Asymptomatic ischemia: resolved issues

1	AI is a clinical syndrome present throughout the spectrum of CAD including chronic stable angina, unstable angina, myocardial infarction and occult CAD.
2	Estimated prevalence and incidence of AI in the US: 2 million with both AP and SI with ~ 75% of episodes silent in 1 million. 50,000 new cases of post MI AI/year.
3	30% of AMIs are unrecognized; 10 to 20% are asymptomatic.
4	Half of all positive exercise tests in patients shortly following AMI are asymptomatic. Prognosis depends on presence of ischemia, not AP.
5	Some patients who experienced sudden death have demonstrated AI on preceding Holter ECG. Some patients resuscitated from sudden death have demonstrated AI post arrest.
6	Mental and emotional stress, physical activity, and cigarette smoking may precipitate AI.
7	AI may be detected by exercise testing, ambulatory (Holter) monitoring, transient myocardial perfusion defects, and transient LV contraction defects.
8	AI as reflected on Holter monitoring demonstrates a circadian variation with an increase in the a.m. Sudden death, AMI and in patients with Prinzmetal's angina, coronary vasoconstrictor tone all exhibit similar circadian variation.
9	In patients with both AI and AP brief episodes of ischemia are usually asymptomatic. Longer and more severe episodes may be symptomatic or asymptomatic.
10	HR is lower when asymptomatic ST segment depression occurs during ambulatory monitoring than during an exercise test.
11	Ambulatory ECG monitoring will detect AI in two groups of patients in whom it cannot be detected by exercise ECG – (1) patients who cannot exercise; (2) Prinzmetal's angina.
12	In a low-risk, apparently healthy population, asymptomatic ECG changes are more often a false positive than true positive finding of ischemia.
13	AI is a predictor of adverse outcome in the asymptomatic, as well as in post AMI, unstable angina and post CABG patients. It is the presence of *ischemia,* rather than whether it is silent, symptomatic or mixed that confers an adverse prognosis.
14	Anti-anginal agents, i.e. beta-blockers, nitrates, and Ca antagonists, reduce the incidence and duration of ST↓ detected on Holter ambulatory ECG monitoring.
15	Successful coronary revascularization (CABG or PTCA) usually abolishes AI.
16	Anti-platelet aggregatory agents such as ASA do not reduce SI, despite reducing TXA_2.

AI = Asymptomatic ischemia; AMI = acute myocardial infarction; AP = angina pectoris; ASA = aspirin; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; HR = heart rate; LV = left ventricular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; ST↓ = electrocardiographic ST segment depression; TXA_2 = thromboxane A_2; VD = vessel disease.

Table 2. Asymptomatic ischemia: unresolved issues – diagnosis

1	Who should be screened for AI? How? When? How often?
2	Does ambulatory (Holter) monitoring add information of diagnostic or prognostic value beyond that obtained from an exercise test?
3	When should ambulatory monitoring be carried out in patients who have positive exercise tests?
4	What is the potential role of on-line solid-state ECG recorders in recognition of AI?
5	When are the costs for further work-up, i.e. catheterization and/or stress thallium scintigraphy justified in asymptomatic patients with abnormalities on ambulatory ECG?
6	Is coronary arteriography generally necessary in totally asymptomatic patients with a low ischemic threshold?

For abbreviations see table 1.

ischemia. The presence of episodes of ischemia, symptomatic and/or asymptomatic, especially when frequent and prolonged, appears to be a predictor of adverse outcome in a variety of patient groups, including patients with stable and unstable angina, post myocardial infarction (especially non Q wave infarction) and following coronary revascularization. Asymptomatic ischemia can be reduced or even eliminated by measures which are known to reduce the incidence, severity and duration of chronic stable angina including drugs (nitrates, beta-blockers and calcium antagonists – alone or in various combinations) and by mechanical revascularization (coronary bypass grafting, coronary angioplasty).

The unresolved issues concerning asymptomatic ischemia may be divided into four major categories: diagnosis, clinical features, prognosis and therapy. In the category of diagnosis (table 2) the key unresolved issues revolve around the question of who should be screened for asymptomatic ischemia, and how this screening should be carried out; the relations between electrocardiograms performed during a standardized exercise test and during ambulatory (Holter) monitoring requires elucidation. Another important unresolved issue is whether (and if so what type of) further work-up is indicated in asymptomatic patients with episodic ST deviations on the ambulatory electrocardiogram.

Among the major unresolved issues in the category of clinical features (table 3) is the question of whether episodes of asymptomatic ischemia become more frequent and/or symptomatic before the development of

Table 3. Asymptomatic ischemia: unresolved issues – clinical features

1	How often do warning symptoms develop before CAD becomes fatal in patients with totally AI?
2	How firm is the evidence that AMI is preceded by increasing AI? What are the implications for monitoring and treatment?
3	What are the clinical consequences of repeated episodes of AI? Is it a risk factor for sudden death and CHF?

For abbreviations see table 1.

Table 4. Asymptomatic ischemia: unresolved issues – prognosis

1	Does ischemia detected on ambulatory monitoring carry with it an adverse prognosis *independent* of coronary anatomy and LV function?
2	Is there a difference in prognosis between AI detected on exercise test vs ambulatory monitoring?
3	Detection of LV dysfunction is more sensitive than ambulatory monitoring in detecting AI. What is the significance of AI reflected in LV dysfunction but not by ambulatory monitoring?
4	Can repeated episodes of AI lead to prolonged but reversible myocardial dysfunction (stunning and/or hibernation), to irreversible myocardial damage, to ischemic cardiomyopathy or to sudden death?
5	Does reduction of AI and/or AP improve prognosis in patients with CAD? In patients post AMI?
6	What is the prognostic significance of demonstrating the ability or inability to suppress AI pharmacologically?

For abbreviations see table 1.

myocardial infarction or death. Perhaps the most important unresolved question in this category concerns the clinical consequences, if any, of multiple episodes of asymptomatic ischemia.

There are a number of important unresolved issues regarding the prognostic features of asymptomatic ischemia (table 4). These include whether asymptomatic ST segment changes detected by ambulatory electrocardiography *independently* confer an adverse prognosis, whether repeated episodes can lead to reversible or even irreversible myocardial dysfunction, whether the ability to suppress asymptomatic ischemia pharmacologically

Table 5. Asymptomatic ischemia: unresolved issues – management

1	Should AI be treated? If so how to what end point?
2	If pharmacologic treatment is carried out to abolish AI won't some patients who should have mechanical revascularization be denied this treatment? Should arteriography precede treatment of AI?
3	Can observations regarding effects of CABG on survival in symptomatic patients, i.e. prolongation of life in patients with 3 VD with impaired LV function be extrapolated to patients with only SI?
4	Should post AMI patients with AI be managed differently from those with AP?
5	If AI is associated with slower HR on ambulatory monitoring than during exercise test, coronary vasodilators, i.e. nitrates and Ca antagonists would be presumed therapeutic agents of choice. Why are beta-blockers so effective?
6	What are the special psychological needs of patients with totally asymptomatic CAD?

For abbreviations see table 1.

is of prognostic significance, and perhaps most importantly whether reduction or abolition of asymptomatic ischemia improves prognosis.

The principal unresolved questions relating to the treatment of asymptomatic ischemia are shown in table 5. The most important is whether asymptomatic ischemia should be treated, and if so under what circumstances, how, and to what end point. Considerable information is available on the effects of coronary artery bypass surgery on the survival of patients with symptomatic ischemia with various anatomic patterns of coronary artery disease and levels of left ventricular function. Is this information applicable to patients with pure or predominantly *asymptomatic* ischemia? Patients with totally asymptomatic ischemia present special psychological problems; on the one hand, some may be especially anxious since they do not possess the normal warning mechanisms when they develop severe ischemia. Ohters are reluctant to accept severe restrictions since they are asymptomatic. Some patients present both of these features simultaneously.

A final, and perhaps the most important unresolved issue is whether asymptomatic ischemia, its detection, evaluation of severity and its monitoring by ambulatory electrocardiography have all been greatly exaggerated. Some critics state that exercise electrocardiography has substantially greater predictive accuracy for asymptomatic ischemia than does ambula-

tory electrocardiographic (Holter) monitoring, except in the relatively small number of patients with Prinzmetal's angina, all or almost all of whom have some episodes of symptomatic ischemia. These critics believe that patients with coronary vascular disease can be selected for revascularization based on the findings on symptoms, exercise electrocardiography, coronary arteriography and left ventricular angiography, and that the presence or absence of asymptomatic ischemia need not affect this important decision.

This monograph enlarges on most of these issues. In subsequent chapters many of the resolved issues are further documented while others are challenged and sufficient light is shed on some unresolved issues so that they may be considered to be well on the way to resolution. Finally, a host of new unresolved questions are identified.

Eugene Braunwald, MD, Chairman, Department of Medicine,
Harvard Medical School and Brigham and Women's Hospital, 75 Francis Street,
Boston, MA 02115 (USA)

Kellermann JJ, Braunwald E (eds): Silent Myocardial Ischemia: A Critical Appraisal. Adv Cardiol. Basel, Karger, 1990, vol 37, pp 7–31

Myocardial Effects of Brief Periods of Ischemia Followed by Reperfusion[1]

Robert B. Jennings, Charles Murry, Keith A. Reimer

Department of Pathology, Duke University Medical Center, Durham, N.C., USA

All myocytes destined to die in the zone of severe ischemia in the dog heart are salvaged by arterial reperfusion if the tissue is reperfused after no more than 15 min of ischemia have passed [1]. This living reperfused myocardium is reversibly injured and differs greatly from control myocardium. The major differences are listed in table 1 together with the duration of time over which the change persists. Some of the alterations last for minutes; others persist for days. In this paper, we shall review these phenomena as they occur in reversibly injured canine myocardium; similar myocardial changes probably occur in the clinical settings of silent ischemia, preinfarction angina, and in cardioplegia.

Occlusion of the circumflex artery in the open-chest anesthetized dog heart results in a large area of ischemia which involves about 30–40% of the left ventricle [2]. The severity of the ischemia varies from heart to heart and in different layers of the ischemic vascular bed in the same heart. The subendocardial layer is usually severely ischemic; collateral arterial flows to this region usually are less than 0.08 ml/min/g of wet tissue in contrast to flows of 0.9–2.5 ml/min/g in control left ventricle [2, 3]. This severely ischemic tissue is the tissue we have used in most of our studies. Although it seems likely that similar changes develop after reperfusion of the moderately ischemic tissue found in the outer wall of the heart, this assumption generally has not been verified by direct study.

[1] This study was supported in part by the National Institutes of Health Grants HL-23138 and HL-27416.

Table 1. Effect of arterial reperfusion on reversibly injured myocytes

1	Reactive hyperemia (minutes)
2	Restore aerobic metabolism and contractile function (minutes)
3	Preconditioning (minutes to hours)
4	Myocardium 'stunned' (hours to days)
5	Adenine nucleotide resynthesis (days)

Metabolic and Functional Effects

Sudden occlusion of a coronary artery in a healthy dog is followed by a marked reduction in arterial flow to the myocardium supplied by that vessel. Within 8–10 s, the oxygen trapped in the tissue as oxyhemoglobin and oxymyoglobin is utilized, oxidative phosphorylation ceases and anaerobic glycolysis supervenes as the only significant source of new high energy phosphate (HEP). At about the same time electrocardiographic changes appear, contractile activity becomes inefficient and shortly thereafter ceases [1, 4] (fig. 1). Most of the creatine phosphate (CP) of the heart is utilized in the first 30–60 s of ischemia [5]. At about the same time, the myocytes begin to swell, as a consequence of the ever increasing load of osmotically active particles (osmolar load) being generated inside the myocytes by ischemic metabolism [6]. Lactate, α-glycerol phosphate (αGP), inorganic phosphate (Pi) and H^+ all increase rapidly. The magnitude of the increases in several representative metabolites is shown in figure 2.

In ischemia, *the demand of the ischemic tissue for HEP exceeds the supply available from reserves (HEP) and from anaerobic glycolysis (AG).* This problem creates many of the metabolic and functional changes detectable in ischemic tissue. Anaerobic glycolysis provides 80% of the HEP utilized in severe ischemia, but is too slow and inefficient to provide the level of HEP required to meet the demand of the ischemic myocytes [4]. The slow rate is due to inhibition of glycolysis by H^+ and lactate and by low levels of oxidized NAD. Glyceraldehyde phosphate dehydrogenase is the chief enzyme inhibited [8]. As net ATP falls, ADP accumulates; its remaining HEP bond can be utilized when 2 molecules of ADP are converted to one ATP and one AMP via the action of adenylate kinase. The resultant ATP is utilized and AMP is dephosphorylated by 5′-nucleotidase to yield adenosine (ADO), which quickly is deaminated via adenosine deaminase to inosine (INO). This results in a decrease in the size of the adenine nucleotide pool (ΣAD). Both ADO and INO diffuse to the extracellular

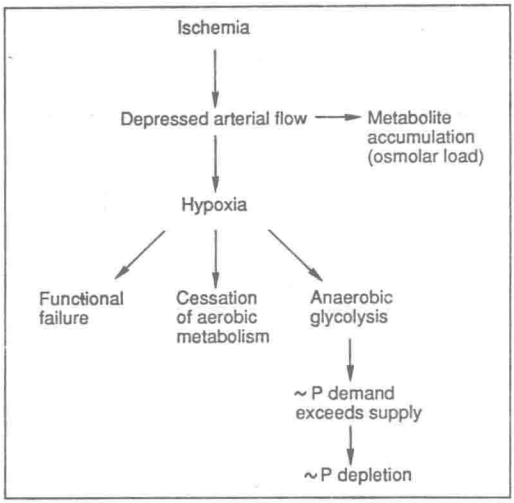


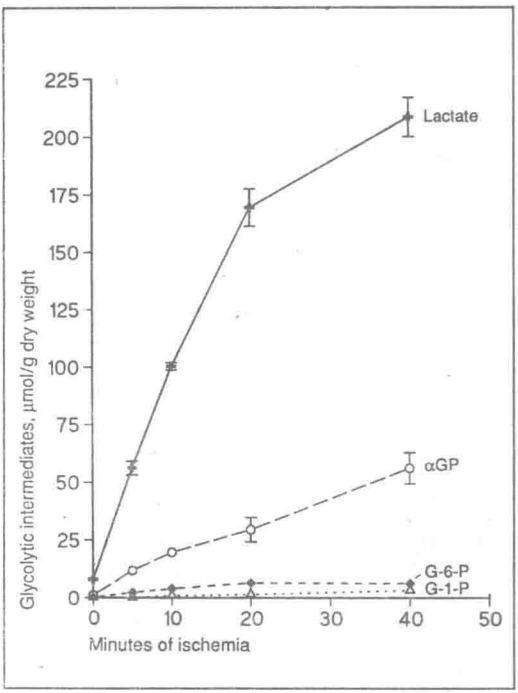
Fig. 1. Some important metabolic consequences of ischemia are shown on this diagram. Metabolites are produced intracellularly by hypoxic metabolism where they accumulate (the osmolar load) and equilibrate to a variable extent with the extracellular fluid. Since the demand of the tissue for HEP exceeds the supply, the net level of ATP falls until it is virtually zero in zones of low-flow ischemia. Reperfusion any time during the first 15 min of ischemia results in return of the metabolite levels to control. It is not known whether they are metabolized when aerobic respiration resumes or are washed to the systemic circulation. [Reproduced with permission of authors and publishers of Ref. 4.]

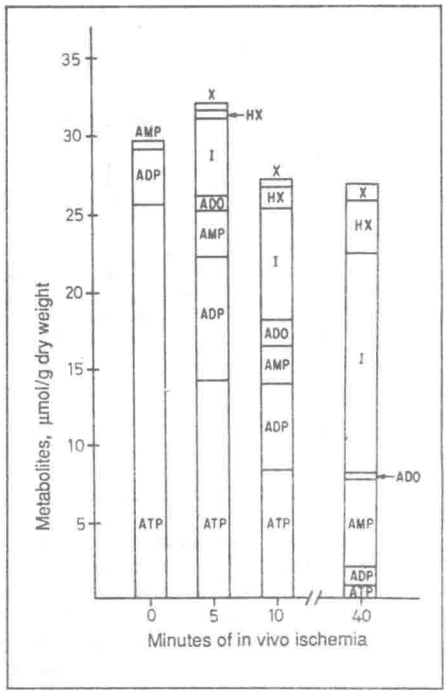
space and are lost from the myocyte [9]. In the extracellular space, both ADO and INO are further degraded to hypoxanthine (HX) and xanthine (X) and no longer can be used to restore the adenine nucleotide pool.

The magnitude of the changes in the adenine nucleotide pool are shown in figure 3. ATP is reduced to one third of control after only 10 min of severe ischemia, and at this point, 50% of the ΣAD has been destroyed.

Effect of Reperfusion of Reversibly Injured Tissue

When the occlusion is opened and blood flow is restored to the cyanotic ischemic myocardium, the first change noted is the development of marked reactive hyperemia. The myocardium develops a 'blush' as the





3

Fig. 2. The rate of accumulation of various glycolytic intermediates as a function of the duration of severe ischemia is shown in this figure. The results were obtained from groups of 4–6 hearts subjected to 5, 10, 20, and 40 minutes of in vivo ischemia. In each case, the arterial collateral flow to the tissue was reduced to less than 0.07 ml/g. The rate of glycolysis, as judged by the accumulation of lactate, slowed after 20 min of ischemia had passed and is known from other studies, to stop shortly after 40 min of ischemia. The source of the glycolytic intermediates is glycogen. At least 25 µmol and as much as 100 µmol of glycogen were present in each of the hearts studied at 40 min, a fact which suggests that substrate deficiency is not a factor in cessation of glycolysis under these conditions.

Fig. 3. Total adenine nucleotide (TAN) pool of ischemic left ventricular tissue is compared with nonischemic myocardium (0 min), ADO, adenosine; I, inosine; HX, hypoxanthine; X, xanthine. The TAN pool is ATP + ADP + AMP. 5 and 10 min of ischemia represent reversible injury. After 40 min of ischemia, the tissue is irreversibly injured. Note that after 10 min of ischemia, the TAN is about 50% of control and that ATP is about 30% of control. [Reproduced with permission of the authors and publishers of Ref. 11.]