SPORT AND ACUTE CORONARY SYNDROMES

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New observations on the pathogenesis of exercise-related acute
coronary heart disease.

Sport en acute coronaire syndromen

Nieuwe inzichten in de pathogenese van acute coronaire hart
ziekten in relatie met sportbeoefening.

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
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Lilian

     Il sole, il mare, la tavola e la dolce lingua d'Italia
     che ti avevano fatto sposare così giovane
     oramai non ti incantavano più. Volevo, dovevo
     seguirti, per vivere l' umida e fredda esperienza
     d'Olanda, dalle melanzane di serra.
     Io lasciavo il tetto familiare ma poi per ben
     cinque volte dovevamo cambiare di casa.
     Tu dovevi rinunciare al lavoro e alla tua specializzazione
     per permettermi di cominciare la mia.
     In tutti questi anni mi hai seguito, tranquilla.
     Per le poche cose che ho fatto, e anche per questa tesi,
     mi sei stata amica, consigliera, dattilografa, secretaria.
     Intanto, quasi da sola, hai cresciuto due figli.
     Hai ragione di dire che siamo ricchi:
     la felicita' di vivere in salute, di avere un figlio
     e una figlia, la famiglia, alcuni veri amici
     e qualche conoscenza del mondo.
     Quanto mi dai, quanto tu hai fatto per me,
     non saro' mai capace di farlo per te.
     Ma un ringraziamento non e' quel che ti aspetti,
     anche se io ti sono grato. Solo ti dico che ti amo
     e che senza te non avrei voluto e potuto essere quel che sono.

``Lilian,
The sun, the sea, the food and the sweet language of Italy, which beguiled
you to marry so young, had lost some of their charms for you. I wanted, I
had to follow you to live out the wet and cold experience of Holland, with
its greenhouse aubergines! So I left the paternal home, but after that we
had the upheaval of five more moves. You had to give up your work and
specialization to allow me to start with mine. During all these years you
quietly followed me wherever I went. In everything I've done, including
this thesis, you've been my friend, my counsellor, my typist, my secretary.
Meanwhile, you raised our two children almost entirely on your own. You are
right in saying that we have been richly blessed: we know the real happi-
ness of good health, we have a daughter and a son, our families, a few true
friends, and some knowledge of the world. So much you gave to me, so much
you did for me; I'll never be able to repay you. But gratitude is not what
you ever sought, though I am truly grateful to you. What I really want to
say is that I love you and that without you I wouldn't and couldn't have
been what I am today.``

                     A Lilian, Metamia e Raymondo,
                     che sono la mia vita; ai miei
                     genitori, che me l'hanno permessa.

Sunt bona, sunt quaedam mediocria, sunt mala plura
quae legis hic: aliter non fit, Avite, liber.

``Avite, some of the pieces you can read here are good, some
are very mediocre, most are bad: there is no other way to make
a book.``

<div align="right">

Martialis (793-858 ab Urbe condita)
Epigrammaton libri I,16.

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CONTENTS

CHAPTER 1

THE PHENOMENON OF SUDDEN DEATH

AND ITS RELATION TO EXCERCISE

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Coronary artery disease accounts for over 50 per cent of cardiovascular deaths and about one third of all deaths in the United States.[1,2] Approximately one in five apparently healthy middle-aged men is at risk of developing an acute myocardial infarction. The atherosclerotic process responsible for the manifestation of coronary artery disease probably begins in childhood.[3] The severity and rapidity of development of atherosclerosis is related to the serum cholesterol level, blood pressure, cigarette smoking, parental history of heart disease and "coronary prone" behaviour (type A).[1,2,4-9] Physical inactivity has also been incriminated as a contributory factor.[10] More recently physical inactivity has been addressed as an independent and modifidable coronary artery disease risk factor.[10A-B] The results of large-scale prevention trials have suggested that lowering risk factors decreases the incidence of fatal and non-fatal myocardial infarction and sudden death, but the possible influence of physical activity was not addressed in these studies.[11-13] Conversely, there is ample epidemiological evidence to suggest that regular exercise protects against coronary artery disease.[14-20] These studies tend to support regular exercise as being a preventive measure and are mainly responsible for increasing participation in recreational and competitive sporting activities observed especially in the USA.[21-25] During the last 25 years, therefore, probably reflecting an increase in leisure time, there has been an enormous rise in the number of middle-aged "coronary prone" individuals engaging in strenuous exercise.[26-33] With this increasing participation in exercise and sports have come a number of reports on sudden deaths during or after strenuous exercise.[27-36]

This paradoxal phenomenon of superior physical performance and unexpected death soon became the concern of public and private sports agencies and the medical profession.

A consistent body of data has been gathered, providing evidence that strenuous exercise could precipitate cardiac death in those with underlying silent or unknown cardiac pathology, primarily coronary

artery disease.[26-42] Consequently, these findings have led to the development of strategies for subject assessment in order to reduce the risk of cardiac death related to exercise.[43-45] However, most of the available studies were conducted retrospectively and all were based on necropsy findings. The mechanisms of these deaths therefore remain merely speculative.[45,46] Furthermore, previous studies focused mainly on sudden cardiac death, which is one aspect only of the spectrum of acute coronary artery diseases.[47]

AIM OF THE STUDY

The present study was undertaken in order to elucidate the pathogenesis of exercise-related coronary events and to determine whether or not there is a direct cause-effect relationship between sport and these events. A secondary objective was to establish whether or not habitual physical exercise also plays a protective role in the development of coronary artery disease. Finally, an attempt was made to identify factors or markers which could help to differentiate sporting from sedentary people with regard to the occurrence of acute coronary events.

STRUCTURE OF THE THESIS

The epidemiology and etiology of exercise-related sudden death are described in Chapter 2. Particular emphasis has been placed on the benefits and risks of exercise, the most relevant reports on sudden coronary death and non-fatal coronary events related to sporting activities. A short critical review of the current hypothetical mechanisms of sudden cardiac death associated with exertion is also supplied. The background of the study, together with the aims and the methodology used, is also reported.

In Chapter 3, the acute coronary angiographic findings of previously healthy people who developed acute myocardial infarction and sudden death after sporting activities are described.

In Chapter 4, the acute coronary angiographic findings of patients with known or suspected coronary artery disease who developed unstable

angina, acute myocardial infarction and sudden death after a (normal) exercise stress test are presented.

In Chapter 5, the clinical characteristics and coronary angiographic findings of previously healthy, well-conditioned people who developed unstable angina, acute myocardial infarction and sudden ischemic death, either during or after sport, are reported.

In Chapter 6, the clinical and coronary angiographic characteristics of healthy subjects and patients resuscitated from exercise-related sudden ischemic death occurring during or after sport and during or after exercise testing are studied.

In Chapter 7, the characteristics and the acute and long-term outcome of a group of well-conditioned men developing an acute coronary syndrome in relation to sport are analyzed in comparison with those of a matched group of sedentary men developing the same acute coronary syndrome at rest.

Chapter 8 gives a general discussion of the findings of the study, its implications and limitations.

Finally, English, Dutch and Italian summaries are supplied.

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CHAPTER 2

EXERCISE, CORONARY ARTERY DISEASE

AND SUDDEN CARDIAC DEATH

HISTORY

In Western Civilization, Hippocrates was the first to describe sudden death over 2000 years ago:[1]

Καρδίης ἄλγημα πρπσβυτέρῳ πυκνὰ ἐπιφοιτέον Θάνατον ἐξαπίναιον σπμαίνει.

"Cardiac angina, more frequent in the elderly, announces sudden death." The first reported case of exercise-related sudden death is associated with the victory of the Athenians over the Persians on the battlefield of Marathon (in 490 BC). A legendary man called Pheidippides or Thersippos or Eukles ran from Marathon to Athens to bring the news of victory over the Persians. The only thing he said was "Joy! We won!" and then he collapsed and died. To commemorate this the marathon run was established in Athens in 1896 during the first mondial Olympic Games.[2,2A] The occurrence of sudden death and its relation to strenuous physical exertion were thus recognized as long as 2500 years ago.

Although during the course of the Christian era the phenomenon of sudden death has occasionally been described or studied in its incidental or epidemic form,[3] it was only at the beginning of the 20th century that coronary arteriosclerosis was recognized as one of its major causes.[4-5]

EPIDEMIOLOGICAL STUDIES

BENEFITS OF EXERCISE

The majority of the studies relating to physical activity - not necessarily strenuous - and the occurrence of sudden death, are observational and retrospective. A relationship between occupational activities and coronary heart disease rates was first observed by Morris and colleagues[6] who reported that physically active London bus conductors and postmen who walked and cycled on the job had lower rates of coronary artery disease and sudden death than sedentary bus drivers and civil servants. Similar findings were reported on farm workers in Iowa,[7] Georgia,[8] North Dakota,[9], postal workers[10-12] and longshoremen.[13-14] A prospective epidemiological study showed that

the incidence of coronary heart disease is lower in rural men in Puerto Rico, who are physically more active than urban men.[15] Multivariate analysis suggested that increased physical activity was a separate protective factor against coronary events. In a retrospective Israeli study,[16] workers in Kibbutzim were simply classified as either sedentary or non-sedentary and were followed during 15 years as to the incidence rates of fatal and non-fatal coronary events. It appeared that the relative risk of coronary artery disease for sedentary men was 2.5 times that for men engaged in work requiring physical activity. The results of the Framingham study[17] were complementary in that they showed that sedentary men were at greater risk of coronary heart disease. Numerous other population studies[18-22] have also shown a direct association between jobs requiring low levels of physical activity and increased risk of myocardial infarction, stroke and overall mortality. In contrast, several other large-scale epidemiological studies[23-26] have shown no relation between physical activity and the manifestation of coronary disease. One study has suggested that habitual vigorous exercise may actually be deleterious to the heart.[27] Furthermore, although the vast majority of the aforementioned studies evidenced an inverse relation between job activity and coronary artery disease, no association was noted either among civil service employees in Los Angeles or among company employees.[28-31] On the other hand, recent studies have provided convincing new evidence that a high level of physical activity protects against premature cardiac and non-cardiac death, even in the presence of all known coronary risk factors.[32-35]

Conversely, as stressed by a review of better designed studies, physical inactivity can be indicated as a modifiable as well as an independent risk factor for coronary heart diseases.[35A-B]

Confounding variables. The results of the above-mentioned studies were invalidated by a series of limitations, including: confounding coronary risk factors that made it difficult to determine the independent role of exercise; difficulties in assessing the level of

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physical activity and in diagnosing coronary artery disease;[36,37] the socio-economic status of the study groups and the related health habits;[38-42] the presence of "coronary-prone" type A behaviour in the sub-groups[43-45] and the possibility of genetically determined "self-selection", whereby healthier persons choose physically active jobs or become sporters.[46-48]

Leisure-time exercise and physical fitness. Recent studies exploring the relation between physical activity and coronary artery disease rate have been focused on the leisure-time activity of workers rather than on job activity. Siscovich and colleagues[49] retrospectively determined that the risk of cardiac arrest was 55 to 65 per cent lower in persons engaged in high-intensity physical activity than in persons engaged in low-intensity physical activity. Paffenbarger et al.[50] analyzed the cardiac outcome of college alumni in relation to the continuation of exercise and sporting activities. College athletes who continued exercising had a diminished risk for coronary heart disease. This study further showed that only current physical activity is associated with reduced coronary heart disease events, even in men who were not particularly athletic but who became active in later life. Conformly, several other studies[51-54] have revealed that middle-aged people engaging in vigorous leisure-time exercise such as jogging, heavy work around the house and garden, or hill climbing, etc., had a significantly (50 to 30%) lower rate of acute myocardial infarction and sudden death than did their sedentary colleagues. Physical fitness has also been correlated with coronary diseases and coronary risk factors.[54] In one study[55] physical fitness status, assessed by bicycle ergometry, appeared to be inversely related to the risk of developing an acute myocardial infarction. This risk was further increased if "below-average" physical fitness was associated with at least two coronary risk factors (e.g. elevated cholesterol and blood pressure or cigarette smoking). Similarly, in another study,[56] those subjects who were unable to exercise for more than six minutes had a significantly

higher rate of primary coronary events within five years. However, this group had at least one or more coronary risk factors. Poor fitness was further addressed as a non-independent predictor of coronary events.[57,58] In one study,[57] it was suggested that the reduction of coronary disease linked with exercise might not be a direct effect of exercise itself in that people engaged in strenuous leisure-time activity had a lower mean serum cholesterol level, lower body weight and blood pressure and smoked less. Another study[58] showed that fitness was inversely related to the most important coronary risk factors.

Exercise and coronary risk factors. Evidence has been provided by both epidemiological and applied physiological studies that exercise favourably affects some or all of the coronary risk factors.[59-68] Exercise might protect against coronary heart disease indirectly by attenuating coronary risk factors such as blood lipids, blood pressure, glucose tolerance and cigarette smoking. Although blood pressure[63] and glucose tolerance appear to be directly influenced by exercise, serum cholesterol levels are clearly dependent on lipids intake.[68] In addition, cigarette smoking seems to be strongly related to personal habits, which in turn can be the expression of "self-selection"[61] for a healthier way of life often encountered in exercisers. This, however, again raises the question as to whether exercisers become healthier persons or healthier persons become exercisers.[69-71] Another important risk factor is a family history of coronary heart disease. In a matched-pair study of marathon runners [72] it was reported that their paternal history of coronary disease was 40% that of non-runners, thus suggesting that the reduced coronary events rate in runners might be due in part to decreased familial predisposition. However, another study[73] showed that a family history of coronary disease increases the incidence of coronary events in both sportsmen and sedentary people. Therefore, exercise does not seem to influence the effects of this important coronary risk factor. "Coronary-prone" behaviour[43-45] has been associated with an increased

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risk of coronary artery disease. However, this risk factor seems modifiable by habitual exercise. Indeed, one study showed that the annual incidence of coronary events in exercising type A men was significantly lower than that of type A men not engaging in regular exercise.[43]

RISKS OF EXERCISE

The occurrence of acute coronary disease and sudden death during or shortly following a sporting performance is a dramatic and newsworthy event. The phenomenon, however, is rare.

Exercise-related sudden death. The incidence of exercise-related sudden death is one jogging death/7,620 joggers,[75-76] one death/50,000 playing hours of rugby,[77] one death/13,000 to 26,000 person-hours of cross-country skiing.[78] Overall, it has been calculated that one fatal event will occur for every 887,526 hours of recreational physical activity.[79] However, it is not known how many of the 1000 sudden deaths occurring daily in the USA[80] are related to strenuous exertion. The authorities do not categorize deaths on the basis of the activity of the deceased before death occurred. Therefore, most reported cases of exercise-related sudden death depend on media reports, which are likely to underestimate the true incidence of the phenomenon, leading by consequence to an incomplete analysis of the problem. In a review of 22 studies[81] of sudden death with either suspected or necropsy-proven coronary artery disease, it was concluded that 11 to 15% of 8,851 reported cases of fatal and non-fatal coronary events were associated respectively with moderate and strenuous exercise. On the other hand, the reported percentage of sudden deaths varies consistently, depending on the volume of the study group. [32,75,77,82-97] A national Registry of sport related sudden death in the Netherlands in the period 1978-1980 revealed an incidence of 103 deaths per year (or 1 death per 45,000 sporters or per 7 million exercise hours).[115 B] According to the preliminary report of a repeat recent national Registry in the Netherlands (1988-1991) the percentage of sport related sudden death has increased reaching the number of 150

death per year.[97A] The explanation for this increased number can be multifactorial : increased participation in sporting activities, improved recognition and registration of cases etc.[97A] Strenuous exertion has not always been incriminated as a cause of sudden death,[96] but most authors agree that it can precipitate cardiac arrest, particularly in those suffering from severe coronary artery disease.[89-97]

Exercise paradox. This view, however, does not fully explain the paradox of exercise, namely that habitual vigorous exercise protects against primary cardiac arrest,[19] but that, if arrest occurs, it is more likely to do so in relation to exercise.[32] This paradox was delineated by Siscovich et al.,[32] who reported that the risk of sudden death during physical activity is higher at any level of habitual activity than during periods of inactivity. Several other authors also reported that the occurrence of sudden death during or shortly after strenuous exertion was higher than in less physically intensive periods.[78,89,91,92,98,99] Other authors have also remarked that the incidence of exercise-related sudden death was almost twice as high as would have been expected by chance or exceeded that occurring during sleep and sedentary work.[89,91,98,100,101] These observations are an indication that vigorous exertion can precipitate but also provoke the occurrence of sudden death.

SUDDEN DEATH IN SPORTERS

With regard to cardiac abnormalities, myocarditis, hypertrophic cardiomyopathy, congenital anomalies of the heart or coronary arteries, heart failure and mitral valve prolapse have been reported causes of death in relation to exercise.[101-111] Coronary heart disease accounts for about 80% of all exercise-related sudden deaths. At least 190 reports of sudden death in sport have appeared in the literature.[75-79,89-97,105,112-115A] In some cases sudden death occurred in previously well-trained athletes who had trained from their youth,[77,95,105,115] but the majority of victims were middle-aged well-

conditioned people who had exercised for one to ten years. The majority of them had at least one coronary risk factor. Prodromal symptoms suggestive of cardiac origin were reported in 10 to 70% of the cases. Necropsy study revealed the presence of severe single- or multiple-vessel disease and, frequently, also myocardial scars. Depending on the technique used, pathological examination of the coronary arteries showed either fresh sub-occlusive thrombus or acute intimal lesion in 15 to 80% of cases. In most cases there was no evidence of recent complete occlusion of the coronary arteries. An extensive study on sudden death in sporters was performed by Dolmans who, during a three-year period (1978-1980), registered in the Netherlands 188 cases of sudden death related to sport. In 93% of the cases the cause of death was attributed to cardiac diseases. However, in 30% of the cases only pathological examination provided a definite diagnosis. In this study 19 previously healthy conditioned men are reported in whom the diagnosis of recent or acute myocardial infarction was made either at autopsy (N=16) or clinically (N=3).Their mean age was 40 years (23-52) and their mean exercise time per week was three hours for at least the preceding four years. Fourteen of them died during sport and the other five within two hours after sport. Prodromal symptoms, referred to by their spouses or relatives,were present in eight (40%) of them. Coronary risk factors (cigarette smoking in 14, hypertension in one and hypercholesterolemia in one) were present in 15 (84%). However, for the majority of them no data were available on blood pressure and cholesterolemia. At autopsy seven (40%) subjects showed a "recent" and six (34%) an old myocardial infarction. Acute myocardial infarction was diagnosed in nine (52%). More than single-vessel coronary disease was present in 64% of the cases, but the extent and severity of the disease was not further specified.

This study showed that young and middle-aged healthy moderately conditioned men with at least one coronary risk factor can unexpectedly develop cardiac arrest in relation to sport. A relevant number (74%) of these victims of sudden death had previously had a

non-clinically manifest myocardial infarction.[1158]

SPORT AND NON-FATAL CORONARY EVENTS

Dealing with pathological data only, the question can arise as to whether the (predominant) finding of severe coronary artery disease is restricted to athletes who died suddenly. A Canadian study reported that about one fourth of non-fatal acute heart disease occurs during some form of physical activity.[111] This study, however, did not deal with sportsmen and there was insufficient information about the extent of coronary disease in the people involved. In the literature there have been occasional case reports on ischemic and non-fatal exercise-related acute coronary events in athletes.

Stable angina pectoris. Ischemic cardiac disease became symptomatic during running in five middle-aged men - well-conditioned runners.[116-118] Four of them were marathon runners, had a paternal history of coronary heart disease and showed severe single-vessel disease at coronary angiography. One case had no coronary risk factors and another had severe two-vessel disease.

Acute myocardial infarction. The occurrence of acute myocardial infarction during or directly after vigorous exertion, such as running or playing football, was reported in ten well-conditioned men aged between 26 and 51 years.[118-126] In six of them there was no detectable coronary risk factor. Coronary angiographic study was performed in all but one and in the acute stage of myocardial infarction in four. In these latter subjects the coronary artery responsible for myocardial infarction was occluded. After administration of a thrombolytic agent there was no detectable obstructive disease of the coronary artery in three cases and a minor stenosis was present in one. In two other subjects respectively, minor and no evident coronary artery disease was found at delayed coronary angiographic study. The remaining three sporters showed severe obstructive single vessel coronary artery disease.

Sudden cardiac ischemic death. Eight sportsmen were reported who were successfully resuscitated from cardiac arrest occurring in relation to sport.[119,127,128,128A] Cardiac arrest occurred suddenly or shortly after the onset of cardiac symptoms. An electrocardiogram following resuscitation showed the development of acute myocardial infarction in 7 subjects. In one of these survivors coronary angiography was acutely performed and showed occlusion of the culprit coronary artery. There was no residual obstruction of the coronary artery after thrombolytic therapy. In 6 other survivors delayed coronary angiographic study showed moderate to severe single-vessel coronary artery disease.

Exercise testing and acute myocardial infarction. Acute myocardial infarction occurring shortly after a controlled normal exercise-stress test was reported in three men and one woman.[129-132] In two men the test was done in order to assess the result of coronary angioplasty procedures performed two and five days earlier.[131,132] Both patients developed chest pain half an hour after completion of a normal exercise test. Acute coronary angiography showed in both occlusion of the previously dilated coronary artery. After failure of reperfusion attempts, both patients underwent acute bypass surgery. In another previously asymptomatic man acute myocardial infarction developed after normal routine exercise testing.[130] Delayed coronary angiography showed occlusion of the culprit coronary artery. Further, exercise was reported to have induced silent acute myocardial infarction by coronary thrombosis in an elderly woman with diabetes mellitus.[129]

Pathophysiology of exercise-related coronary events. The aforementioned findings of at least 213 middle-aged subjects show that coronary artery disease is associated with acute myocardial infarction and sudden death related to vigorous exertion. The predominant necropsy finding of severe obstruction but non-occlusion of coronary arteries has led to the speculation that malignant ventricular arrhythmias, induced by ischemia - either with or without the occurrence of coronary spasm - during exertion, could be the cause of sudden cardiac

death in most of the victims studied.[133] Similarly, cardiac
arrhythmias following reperfusion of previously ischemic areas was
postulated as the cause of sudden death in the post-exercise period.
[133] The hypothesis of ventricular arrhythmias was supported by a
series of indirect evidence that exercise, by way of a rise in serum
catecholamines, potassium, free fatty acids, or their interaction,
could lead to the development of cardiac arrhythmias, particularly in
cigarette smokers.[133] In contradiction to this hypothesis, it has
been shown that, although healthy sportsmen have variations in heart
rhythm and some degree of arrhythmias, these cannot be considered as
malignant or dangerous.[134-138] Furthermore, studies of survivors of
cardiac arrest have generally not observed any relation between the
onset of ventricular arrhythmias and physical exertion.[139] Life-
threatening arrhythmias, such as sustained ventricular tachycardia and
ventricular fibrillation, rarely occur during exercise testing in pat-
ients with coronary artery disease, even when ischemia is present.[140-
141] As far as non-fatal coronary events associated with exertion are
concerned, in about 50% of cases coronary angiography showed single-
vessel disease, and in some cases there was no evident residual
stenosis in the culprit coronary artery after reperfusion with throm-
bolytic therapy. This finding indicated the presence and prevalence
of thrombosis; a feature which associates these sporters with the
general population of patients with an acute myocardial infarction.
The prevailing opinion of the authors of the reported cases was that a
vigorous exercise programme fails to prevent coronary atherosclerosis
and coronary events. One author[117] remarked that daily exercise was a
positive habit which can "unmask" pre-existent coronary artery disease
at an earlier stage. Although exercise was suspected as being contri-
butory to the occurrence of the acute coronary event, the mechanism
remained uncertain. Some authors [120,126,129,130] hypothesized the
occurrence during exercise of a dynamic interaction between high
coronary flow, shear stress, damaged intima, platelet aggregation and
coronary artery spasm leading to coronary thrombosis. Other authors
[122-125] related the occurrence of acute myocardial infarction to chest-

trauma caused by a football on the chest. Such a "trauma", however, is very common in experienced soccer players and is certainly not comparable with that provoked by an automobile accident.[142] The cause of the acute coronary event was not taken in association with physical exertion.

Limitations of previous studies. Existing epidemiological studies strongly suggest that habitual exercise offers protection against coronary artery disease and associated mortality. However, the interaction between multiple factors in the development and manifestation of coronary heart disease and the unfeasibility of extensive clinical trials make it difficult to achieve definitive proof of the role played by physical exercise. Furthermore, paradoxically, epidemiological studies and some case reports also suggest that strenuous exercise precipitates or provokes acute coronary events and sudden cardiac death. The most probable explanation for this paradox is the pre-existence of severe coronary artery disease in those subjects who develop an acute coronary event in relation to exercise. Therefore, physical exertion should play merely a precipitating coincidental role in the manifestation of these events. Previous studies, however, present a series of limitations. The terms "strenuous exercise" and "habitual exercise" are not in most cases further specified. Very often, the level of physical training of the subjects involved and the time span of their effective training are not clear. Furthermore, the hypotheses and conclusions of previous studies were based mainly on necropsy findings. Moreover, necropsy study was not performed in all reported cases, the techniques used to examine the coronary arteries were not always comparable and the diagnosis of "coronary death" was not always based on necropsy or clinical data. In addition, important clinical information, such as level and time span of physical training and prodromal cardiac symptoms, were collected from the testimonies of the spouses or relatives of the victims. Finally, with the exception of a few well-documented case reports on non-fatal exercise-related coronary events, previous

studies concentrated only on the phenomenon of sudden death. However, it is likely that the spectrum of clinical coronary syndromes, stable and unstable angina, acute myocardial infarction and sudden death, may also be manifest during and immediately after strenuous exertion.

BACKGROUND, AIMS AND METHODS OF THE PRESENT STUDY

Clinically unstable angina, acute myocardial infarction and sudden cardiac ischemic death are defined as acute coronary syndromes. Pathological studies have demonstrated that these syndromes are the manifestation of a series of intracoronary dynamic processes derived from fissuring or rupture of an atherosclerotic plaque.[143-146] Plaque rupture can lead, by intra-intimal and/or intracoronary thrombosis, and with subsequent coronary spasm and thromboembolism, to coronary (sub)occlusion.[5,146] Necropsy and angiographic studies have shown that the most frequent finding in patients with unstable angina, acute myocardial infarction and sudden ischemic death is a (sub)occlusive thrombus and that very often an eccentric lesion, consistent with plaque rupture, is found in the culprit coronary artery.[143-152] Therefore, plaque rupture is now considered to be the most likely mechanism responsible for the initiation, progression and acute manifestation of the three acute coronary syndromes.

It was hypothesized that a similar spectrum of acute coronary syndromes might occur in relation to sporting activities (strenuous exertion) and that the underlying mechanism would be the same.[153] The primary aim of the study, therefore, was to collect and analyze the clinical characteristics and the (acute) coronary angiographic findings of well-conditioned subjects developing an acute coronary syndrome associated with sport, in order to elucidate the mechanism(s) of these events. Analyzing these data, it might also be possible to establish a cause-effect relationship between strenuous exertion and acute coronary syndromes. This would suggest that exercise (and its physiologic changes) is directly responsible for the occurrence of these syndromes. During the period between 1984 and 1990 data were collected on previously healthy subjects – well-conditioned and

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habitually sporting since their youth – who were admitted to three
institutions with the diagnosis of unstable angina, acute myocardial
infarction or were resuscitated victims of sudden cardiac ischemic
death occurring during or within one hour[133] after sporting
activities. The three institutions were located in the proximity (2
to 8 kms) of sports fields and sporting centres. In addition, an
attempt was made to determine whether habitual exercise differentiates
physically active from sedentary people apart from the provocation of
an acute coronary syndrome. In order to do so, the characteristics of
a matched group of sedentary people developing an acute coronary
syndrome at rest were compared with those of the sporting group.
Finally, during the same period, the data of patients developing an
acute coronary syndrome related to exercise testing were also
collected and analyzed. In connection with the pathophysiology of
exercise-related coronary events, the occurrence of an acute coronary
syndrome related to a supervised exercise test can be regarded as a
semi-experimental situation, allowing important clinical and
electrocardiographic information to be obtained and studied.The popu-
lation studied comprised 57 previously healthy well conditioned sub-
jects and 50 patients. Definitions, treatment procedures and analysis
of clinical, laboratory and angiographic data are extensively reported
in the following chapters.

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CHAPTER 3

MYOCARDIAL INFARCTION AND SUDDEN DEATH AFTER SPORT:
ACUTE CORONARY ANGIOGRAPHIC FINDINGS

Recurrent Myocardial Infarction and Sudden Death
After Sport

Original Studies

Myocardial Infarction and Sudden Death After Sport: Acute Coronary Angiographic Findings

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Thirteen patients, seven with acute myocardial infarction and six survivors of sudden death after sport, underwent coronary angiography within a mean of 104 min after the onset of symptoms. The admission electrocardiogram showed transmural myocardial ischemia in all patients.

The ischemia-related vessel was occluded in all cases of sudden death and in three cases of acute myocardial infarction. Reperfusion was achieved in eight vessels: after intracoronary streptokinase in three, after intracoronary nitroglycerin in three, and mechanically in two. Coronary spasm was demonstrated in three vessels, and coronary thrombi, in four. The coronary lesion was described as either concentric in two or eccentric with irregular borders in eight. There was a high incidence of eccentric lesions consistent with ruptured plaques.

The acute coronary angiographic findings of acute myocardial infarction and sudden death after sport are similar. Physical exercise can provoke myocardial infarction and sudden death probably by inducing plaque rupture that can evoke coronary spasm, thrombosis, or both.

Key words: coronary angiography, plaque rupture, physical exercise

INTRODUCTION

The phenomenon of acute myocardial infarction (AMI) and sudden death (SD) related to sport is well known, but most of our present knowledge is based on necropsy observations. Therefore, the pathophysiology of these events is still hypothetical [1–8]. We report the acute coronary angiographic findings of seven patients admitted with AMI and of six survivors of SD that occurred after sporting activities. These findings may help in understanding the pathophysiology of coronary events related to physical exercise.

MATERIALS AND METHODS

The diagnosis of AMI was made when continuous chest pain was present, with typical electrocardiographic (ECG) signs of transmural myocardial ischemia defined as ST-segment elevation and/or depression of 2 mm or more in two or more contiguous leads [9], unrelieved by nitroglycerin (NTG) administration. Sudden death (SD) was defined as being witnessed death that occurred suddenly, with or without preceding symptoms, within the first hour after exercise [8].

In the period between July 1984 and March 1987, 13 consecutive patients were admitted to our institution with the diagnosis of AMI or as resuscitated survivors of SD

that occurred after sporting activities. All these previously healthy subjects had exercised regularly since their youth (cycling, jogging, soccer, volleyball) and had participated at least once a month in amateur sporting competitions. Patients with AMI were eligible for coronary angiographic study if they had been admitted within 3 h after the onset of symptoms. Survivors of SD were eligible if 1) cardiopulmonary resuscitation was started directly after the onset of SD; 2) the ECG after resuscitation showed acute transmural myocardial ischemia, 3) the blood pressure and rhythm were stable after resuscitation, and 4) the time between onset of symptoms or collapse and admission was not longer than 3 h. Exclusion criteria were age over 70 years; previous treatment

TABLE I. Characteristics of Patients With Acute Myocardial Infarction (AMI), and Sudden Death (SD) After Sport

No.	Clinical presentation	Sex	Age (yrs.)	Smoker	Sport (hr/w)	Prodromata	Time to CAG
1	AMI	M	42	Yes + − −	4	No	165
2	AMI	M	41	Yes +	4	No	60
3	AMI	M	65	No	15	No	80
4	AMI	M	47	Yes +	3	Yes	145
5	AMI	F	42	Yes + +	2	No	170
6	AMI	M	48	Yes + −	3	No	60
7	AMI	M	49	Yes +	4	No	200
1	SD	M	49	Yes + + +	7	No	70
2	SD	M	37	Yes + +	3	No	90
3	SD	M	34	No	10	No	60
4	SD	M	37	Yes + +	3	No	95
5	SD	M	50	Yes +	8	Yes	90
6	SD	F	55	Yes +	4	No	100

Abbreviations: Yes + = 10; + + = 20; + + + = 30 cigarettes a day; hr/w = hours/week; CAG = coronary angiography after onset of symptoms, in min.

TABLE II. Acute Coronary Angiographic Findings in Patients With Acute Myocardial Infarction (AMI), and Sudden Death (SD) After Sport

No.	Clinical presentation	CCA	Patent	Reperfusion	Morphology of lesion	Thrombus	ACD
1	AMI	LAD	Yes	—	E.I.	Yes	No
2	AMI	RCA	No	Yes, NTG i.c.	E.I.	Yes	OM 100%
3	AMI	OM	No	Yes, mech.	?	?	RCA 50%
4	AMI	RCA	Yes	—	E.I.	Yes	No
5	AMI	LAD	No	Yes, mech.	?	?	No
6	AMI	RCA	Yes	—, SK i.v.	E.I.	No	No
7	AMI	OM	Yes	—	E.I.	No	No
1	SD	LAD	No	Yes, SK i.c.	E.I.	No	No
2	SD	LAD	No	Yes, SK i.c.	C.	No	No
3	SD	Cx	No	Yes, SK i.c.	C.	No	No
4	SD	LAD	No	Yes, NTG i.c.	E.I.	Yes	RCA 30%
5	SD	LAD	No	Yes, NTG i.c.	E.I.	No	RCA 100%
6	SD	LAD	No	No	?	?	RCA 40%

Abbreviations: CCA = culprit coronary artery; ACD = associated coronary disease; % = percent of stenosis; LAD = left anterior descending artery; RCA = right coronary artery; Cx = circumflex artery; OM = obtuse marginal branch; SK = streptokinase; i.c. = intracoronary; i.v. = intravenously; NTG = nitroglycerin; mech. = mechanically; E.I. = eccentric irregular; C. = concentric.

with streptokinase (SK); enhanced risk of bleeding; pregnancy; or recent cerebrovascular accident. Prolonged cardiopulmonary resuscitation did not constitute an absolute contraindication for the study [10]. Informed consent was obtained from the patients or their relatives.

Prior to coronary angiography, all patients received intravenous NTG (15 μg/min), heparin (5,000 IU), dexamethasone (12 mg), acetylsalicylacid (500 mg), and lignocaine (100 mg), and then the ECG was repeated. A decision on whether to administer intravenous SK (1.5 × 10^6 IU in 30 min) prior to coronary angiography, in order to reduce delay in treatment, was left to the discretion of the investigator. If the ischemia-related coronary artery appeared to be occluded or subtotally obstructed with grade I flow (TIMI classification) [11], 200 μg NTG were administered intracoronary, followed

by a repeat contrast injection. If occlusion persisted, intracoronary infusion of SK was started at a rate of 5,000 IU/min until reperfusion was achieved or a total of 250,000 IU was given. Mechanical reperfusion was directly attempted in case of failure of intracoronary SK therapy.

The presence of coronary spasm [12] was deduced after administration of intracoronary NTG resulted in 1) opening of a previously occluded coronary artery or 2) a dramatic improvement in the diameter and flow grade of a subtotally obstructed coronary artery (i.e., from flow TIMI grade I–III). Intracoronary filling defects were defined as being consistent with thrombi if they appeared spherical, ovoid, or irregular outlined by the contrast medium [13]. Morphology of coronary artery lesions was described following the classification of Ambrose et
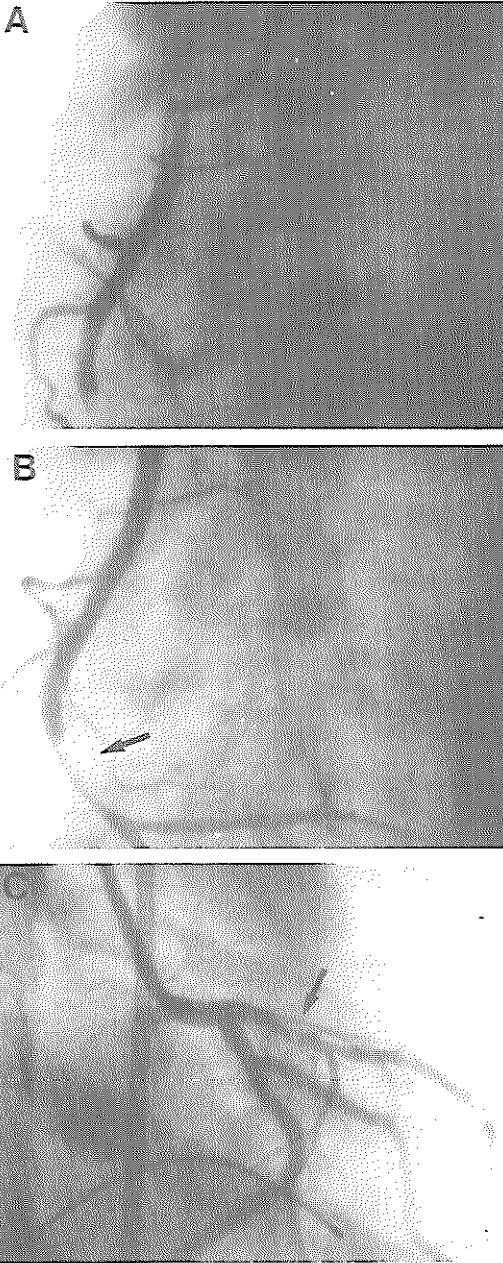
Fig. 1. A: Patient 2, with acute myocardial infarction. Right coronary angiogram, showing proximal occlusion. B: The occlusion is relieved after 200 μg nitroglycerin intracoronary; an eccentric lesion with irregular borders and intracoronary thrombi are visible at the site of previous occlusion. C: Patient 1, survivor of sudden death. Left coronary angiogram, showing an eccentric irregular lesion in the left anterior descending artery (see arrow) after reperfusion with intracoronary streptokinase.

al. [14] as either concentric or eccentric with regular (type I) or irregular (type II) borders. All ECGs and coronary angiograms were reviewed independently by three experienced cardiologists. Before discharge from the hospital, all patients answered a questionnaire concerning symptoms prior to their cardiac accident. [15].

RESULTS

Thirteen patients were studied, seven with AMI and six survivors of SD. Their clinical characteristics and acute coronary angiographic findings are listed in Tables I and II, respectively. The mean age of AMI was 47.7 years, and for SD, 38.7 years. Apart from their smoking habits, patients 1, 4, 5, and 6 with AMI also had a family history of coronary artery disease. Patient 7 of AMI had a previous history of mild untreated hypertension. Cholesterol and triglyceride levels were normal in all. Prodromal symptoms suggestive of anginal complaints were present in two patients. The average time per week spent on sporting activities was 5 h for AMI and 5.8 h for SD. The mean interval time between end of sporting activity and onset of symptoms was 40 min (range 10–60) for AMI and 30 min (range 10–45) for SD. Three of the six survivors of SD (patients 2, 3, 5) collapsed suddenly without previous symptoms. The remaining three collapsed within 15 min after the onset of symptoms. The direct cause of SD was ventricular fibrillation in five and asystole in one. The mean time between the onset of symptoms and coronary angiography was significantly shorter for survivors of SD (84 min) when compared with that of patients with AMI (120 min). This difference was because victims of SD reached the hospital more quickly. The ischemic localization on the ECG corresponded in all cases with the ischemia-related coronary artery.

At coronary angiography, all but one survivor of SD showed involvement of the left anterior descending artery. The culprit coronary artery was found patent in four out of seven cases of AMI (one of which after intravenous administration of SK) and was occluded in all cases of SD. Reperfusion after intracoronary administration of NTG, indicating the presence of vasospasm (Fig. 1A,B), occurred in three cases, one of AMI and two of SD. Reperfusion was further achieved in five more vessels, after intracoronary administration of SK in three, and mechanically in two. All patients except one survivor of SD developed a myocardial infarction as determined by enzymes and ECG changes. Coronary morphology of the lesion was determined in ten vessels without occlusion directly or after the administration of NTG or SK. Concentric lesions were present in two cases of SD. Type II eccentric lesions were found in eight cases, five of AMI and three of SD (Fig. 1C). Intracoronary thrombi were detected in four vessels,

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initially patent coronary arteries, or after reperfusion with SK or NTG (Fig. 1B). Coronary angiography revealed further minor disease in three cases. In two other cases, a coronary artery was occluded but completely filled by collaterals. There were no complications related to performing acute coronary angiography and coronary reperfusion measures.

DISCUSSION

This study has shown that the acute coronary morphology and findings in patients with AMI and SD after sport are similar. The pathophysiology of exercise-related coronary events is still speculative, and there is no clear explanation for the delayed onset of symptoms or SD following sporting activities. Is there a causal relation between sport and coronary accidents that ensue after physical exercise?

Numerous previous studies reported the occurrence of SD either during sport or within 1 h after sport in people both with and without previous symptoms [1–8]. Before SD occurred, the diagnosis of AMI was made in only a few patients [1,7]. Nevertheless, a direct cause-effect relationship between the preceding sporting activities and the subsequent AMI and/or SD was postulated. Sport was pointed out to be a potential precipitating factor of SD mainly in subjects with known or asymptomatic severe coronary artery disease [2,3]. The most usual finding on pathological examination was severe obstructive coronary disease, often in the presence of healed myocardial infarcts [1–8]. However, complete occlusion of a coronary artery was rare. It was therefore hypothesized that, while coronary spasm could be the cause of SD during sport, cardiac arrhythmias resulting from reperfusion of ischemic areas during sport could well be responsible for SD after sport [8]. Although this hypothesis may be valid in the case of SD within a few minutes after the end of sport, it loses its credibility when the onset of AMI or SD is delayed by up to 1 h after sport. The occurrence of AMI after a normal exercise stress test was reported in three patients [16–18]. In two cases, coronary angiography was acutely performed. This showed coronary occlusion due to thrombosis in one case and thrombosis and vasospasm in the other [17,18].

In the present study, coronary thrombosis, spasm, or both were responsible for coronary occlusion in five out of six patients with SD. In a single case, the cause of occlusion remained undetermined. In the AMI group, indirect evidence supports thrombosis as being the cause of occlusion in three cases and vasospasm in one. Although the vessel was patent in the remaining three cases, intracoronary thrombi were demonstrated in two. In addition, study of the coronary morphology showed predominance of eccentric lesions (type II) in both AMI and SD. This kind of lesion has been correlated by post-mortem coronary angiography with the pathological finding of plaque rupture with or without intraluminal thrombus or intimal hemorrhage [14,19]. Recent clinical angiographic studies in patients with unstable angina and AMI have suggested the same correlation [14]. Plaque fissuring or rupture with a variable degree of intimal hemorrhage and luminal thrombosis was found on necropsy in up to 95% of patients with unstable angina and AMI who died suddenly [20,21]. Therefore, plaque rupture, by reason of its potential development of coronary thrombosis, thromboembolism, and eventually spasm, was postulated as the pathological substrate of unstable angina, AMI, and SD [20,21].

Platelets have been implicated in the pathophysiology of acute coronary syndromes. There are, however, conflicting reports about the role of exercise-related platelet activation and release of vasoactive substances that may cause coronary vasospasm [22–24]. Vasospasm has been shown to play a role in the manifestation of coronary artery disease [12]. Vasospasm was found at the site of coronary occlusion in three patients in this study. This finding, however, does not imply that vasospasm was the primary cause of AMI or SD in some patients. Coronary spasm has frequently been demonstrated as being secondary to intimal damage [12,25–28]. Coronary spasm has also been demonstrated during exercise in patients with variant and classical angina [12,29,30]. The mechanism of exercise-induced vasoconstriction of diseased segments of coronary arteries could be related to unopposed α-adrenergic stimulation by circulating catecholamines due to local endothelial dysfunction [30,31].

It can be hypothesized that during exercise repeated coronary vasoconstriction at the site of an atherosclerotic plaque could lead to rupture of the plaque, which, in turn, could initiate a series of dynamic intracoronary changes leading to AMI and/or SD. Furthermore, since the process initiated by plaque rupture can have a relatively long evolution time before a clinical manifestation appears, this could explain the delay between the end of sport and the onset of symptoms or SD [32].

The pathological observation that sub-/occlusive intraluminal thrombosis or intimal hemorrhage can occur at the site of fissuring or rupture of atherosclerotic plaques involving a mean of 50% or less of the vessel diameter is noteworthy [21,33]. This means that rupture can occur in plaques that are not expected to provoke clinical symptoms [21]. Therefore, we suggest that the lack of prodromal symptoms in most of our patients could be attributed to the absence of significant coronary stenosis prior to the coronary accident related to physical exercise. We were able to substantiate this hypothesis in a patient who developed AMI with subtotal obstruction of a previously normal coronary artery after a normal exercise stress test [18]. Finally, the predominance of intimal hemorrhage may also explain the failure of coronary reperfusion measures in one of our patients [21,34].

This study does not exclude the possibility that the relation between sport and the occurrence of AMI and

SD may have been merely coincidental. Furthermore, the data presented deal only with coronary events after sport related to acute myocardial ischemia.

CONCLUSIONS

The findings at acute coronary angiography in patients with AMI and SD after sport were similar. The predominant characteristic was an eccentric coronary lesion that is consistent with plaque rupture. It is likely that physical exercise can provoke AMI and SD by inducing plaque rupture, which can lead to coronary thrombosis, spasm, or both. Further studies are needed to validate this hypothesis.

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Recurrent myocardial infarction and sudden death after sport

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The occurrence of acute myocardial infarction (AMI) and sudden death (SD) after sport in previously asymptomatic individuals is well known but the pathogenesis of this phenomenon is still hypothetical. We report the unique case of a patient who experienced two episodes of AMI and one of SD after sporting activities. The acute coronary angiographic findings in this case can be helpful in understanding the mechanism(s) of AMI and SD after sport.

A 34-year-old man was seen at the emergency room on July 15, 1981, because of breathlessness and chest pain that occurred 30 minutes after a football match. Being a member of a veterans club, he played football three times a week and exercised regularly on a racing bicycle. He smoked 30 cigarettes a day, but there were no other risk factors. On admission, physical examination, routine blood investigation, and chest x-ray films were normal. The electrocardiogram (ECG) showed 2 mm ST-T elevation in leads V_1 to V_3. He developed a non-Q wave anterior myocardial infarction with a peak serum creatine kinase (CK) of 700 U/L (normal up to 120 U/L). Coronary angiography (CAG) 20 days later (Fig. 1, A) showed no evident obstructive disease in the left and right coronary arteries. After discharge, a maximal exercise stress test was normal. The patient resumed his sporting activities and stopped smoking.

On August 7, 1984, at 2 PM, about 30 minutes after playing football, he suddenly fainted. Onlookers immediately started cardiopulmonary resuscitation. Ambulance personnel at 2.10 PM monitored ventricular fibrillation, and he was promptly defibrillated. On admission, physical examination revealed a comatose slightly cyanotic man with inadequate spontaneous respiration. The pulse was regular at 80/min, and the blood pressure was 120/80 mm Hg. Mechanical ventilation was initiated. The ECG showed 2 mm ST-T elevation in leads II, III, aVF and in V_4 to V_6. The chest x-ray film was normal. In view of AMI,
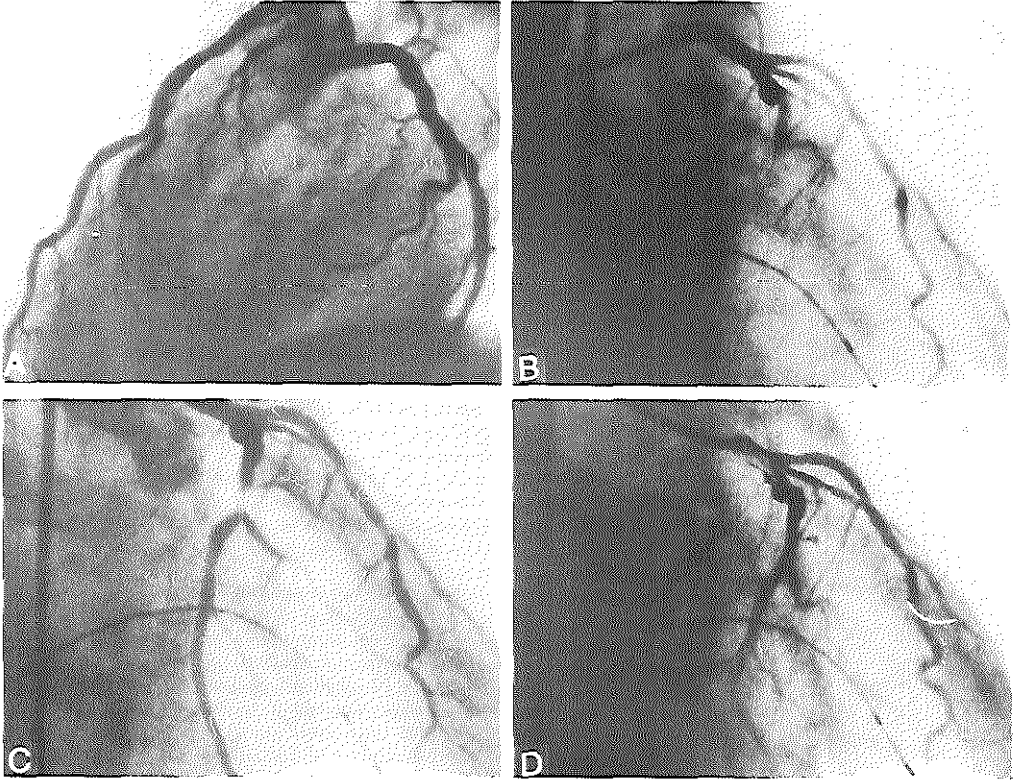
Fig. 1. A, Left coronary angiogram 20 days after a non-Q wave anterior myocardial infarction without evident abnormalities. B, Three years later, 60 minutes after resuscitation from sudden death, showing proximal occlusion of the circumflex artery. C, Fifteen minutes after intracoronary infusion of streptokinase, reperfusion has been achieved; there is a subtotal concentric stenosis. D, After angioplasty of the segment, a steerable guide wire is still seen in the circumflex artery.

CAG was performed at 3.10 PM. This disclosed proximal occlusion of the circumflex (Cx) artery (Fig. 1, B). No change occurred after intracoronary administration of 200 μg of nitroglycerin. Streptokinase was infused by the intracoronary route at a rate of 5000 U/min. Reperfusion resulted after 15 minutes (Fig. 1, C). Transluminal balloon angioplasty was then successfully performed (Fig. 1, D). The patient developed an inferoposterolateral infarction (peak CK 1366 U/L). The ECG showed small Q waves in leads II, III, and aVF. There was complete resolution of his neurologic impairment 2 days after admission. There were no cardiac complications. He recovered and was discharged on oral anticoagulant therapy with a coumarin derivative and pindolol (10 mg a day). Repeat CAG (Fig. 2, A) 3 months later showed no evident obstructive lesion at the site of the previous occlusion. During follow-up, repeat bicycle exercise tests were normal.

On July 22, 1986, he was readmitted because of chest pain that started about 20 minutes after a bicycle race. The ECG on admission showed acute anterior transmural ischemia. CAG was performed 70 minutes after onset of pain and disclosed a subtotal obstruction in the left anterior descending artery (LAD) (Fig. 2, B). There was no change after the administration of intracoronary nitroglycerin. Urokinase was then infused via the intracoronary route at a rate of 10.000 U/min. After 20 minutes there was a decrease in flow across the obstruction and poor distal coronary filling. Balloon angioplasty was then immediately performed (Fig. 2, C). After the procedure, the ECG normalized. There was a maximal CK rise of 180 U/L. He was mobilized and discharged on therapy with aspirin, 80 mg a day. In October 1987, control CAG showed no evident obstructive disease in the Cx and LAD (Fig. 2, D). The left ventriculogram showed localized apical hypokine-
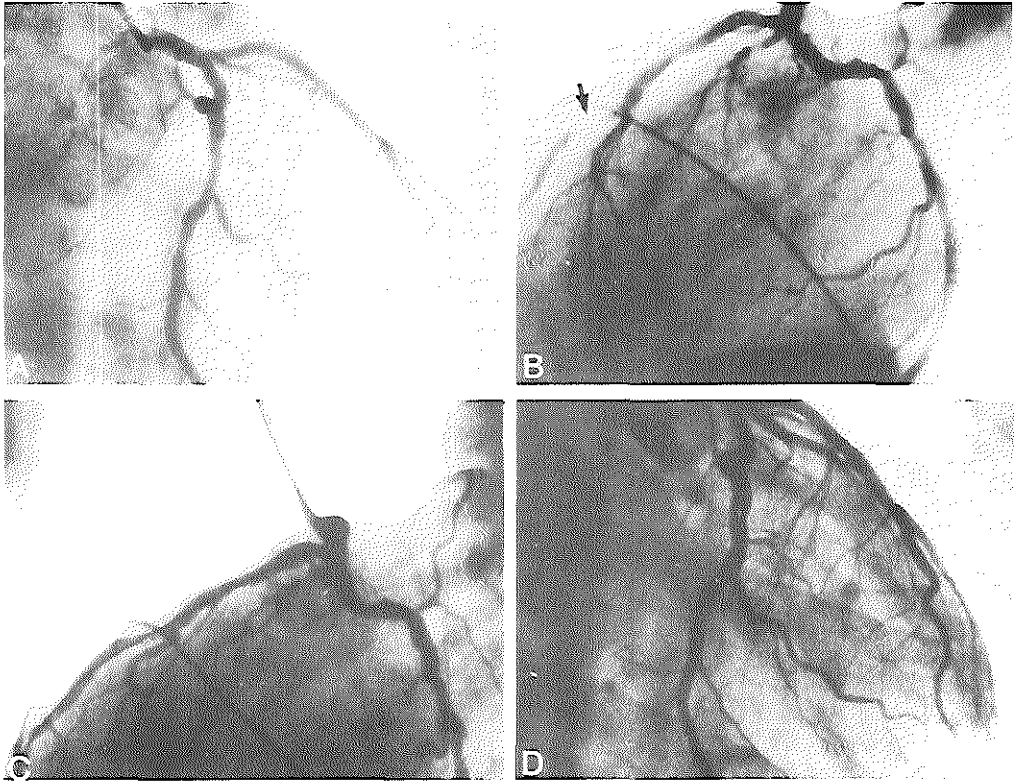
Fig. 2. A, Left coronary angiogram 3 months after angioplasty, showing slight lumen irregularities at the site of previous occlusion. B, Two years later, 70 minutes after onset of pain, showing a subtotal obstruction half way down the course of the left anterior descending artery (arrow). C, After angioplasty of the obstructed segment. D, Four months after angioplasty, showing no evident obstructive coronary disease.

sia. The ejection fraction was 70%. During 22 months of follow-up, repeat exercise stress tests were normal.

Although numerous studies have reported the occurrence of AMI and SD precipitated by sport, acute coronary angiographic findings are lacking under these circumstances. The pathophysiology of AMI and SD related to sport is still unsettled.[1] Necropsy studies have documented that coronary disease is the most usual finding in SD associated with sport.[1] In one case,[2] coronary thrombosis was suggested as the cause of AMI after an exercise stress test. Coronary spasm has also been suggested to be the trigger responsible for SD after sport. However, although coronary spasm has been documented[3] during or shortly after exercise, a delayed onset has never been described. In recent necropsy studies,[4] it has been demonstrated that fissuring or rupture of atheromathous plaques, which can lead to intimal hemorrhage and coro-

nary thrombosis and/or spasm, can represent the anatomic substrate of unstable angina, AMI, and SD. In a previous angiographic study[5] we proposed that plaque rupture could be the etiologic factor of AMI and SD after sport. In the present case, coronary angiography was not performed acutely on admission at the time of the patient's first AMI. The episode of SD was shown to be related to coronary occlusion of the Cx. Reperfusion after streptokinase indicated the presence of coronary thrombosis. The second AMI was due to subtotal obstruction of the LAD. During infusion of urokinase, coronary flow worsened, indicating progression of the obstruction. Hypothetically this may be due to an increase in thrombus formation despite a thrombolytic agent. On the other hand, it is unlikely that primary thrombosis could occur in a patient on chronic anticoagulant therapy. A more likely explanation could be provided by a ruptured plaque with

intimal hemorrhage leading to subtotal coronary obstruction.[4,6] The presence of coronary spasm could not be proved in this patient.

This report presents several unique features. First, the recurrence of AMI and the episode of SD after sport in the same patient has never been previously reported. This case demonstrates a relation between sport and coronary events that cannot further be referred to as "merely coincidental." Additionally, although reperfusion arrhythmias have been implicated in the occurrence of SD after sport,[1] this construction seems improbable when, as in our case, SD is delayed. Finally, coronary thrombosis alone cannot satisfactorily explain the angiographic findings in our patient. According to recent observations,[4] either coronary thrombosis and/or spasm with or without occlusion can be the possible manifestations of the same anatomic pathologic substrate represented by plaque rupture. Although definitive proof can only be obtained at necropsy,[4,6] we suggest that exercise-precipitated plaque rupture with intimal hemorrhage with or without coronary thrombosis and/or subtotal coronary occlusion can explain both the angiographic findings of the recurrent AMI and SD in our patient.

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CHAPTER 4

UNSTABLE ANGINA, MYOCARDIAL INFARCTION AND SUDDEN DEATH AFTER AN EXERCISE STRESS TEST

Exercise-Induced Plaque Rupture Producing Myocardial Infarction

Unstable angina, myocardial infarction and sudden death after an exercise stress test

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We performed coronary angiography within 95 minutes of the onset of symptoms in seven patients with an acute coronary event after an exercise stress test. The test was normal in six patients. Previous angiography in four patients revealed no evident or moderate obstructive coronary arterial disease. After the test, unstable angina developed in two patients, acute myocardial infarction in four and ventricular fibrillation in one, who was successfully resuscitated. At acute angiography the coronary artery involved was occluded in four and sub-totally obstructed in three. In three cases, coronary occlusion was due to thrombosis, vasospasm, or both. In six vessels there was an eccentric lesion, which is consistent with a ruptured plaque. These findings show that physical exercise can unexpectedly provoke an acute coronary event with sub-total or total occlusion of a previous angiographically normal or moderately obstructed coronary artery. The mechanism is probably related to exercise-induced plaque rupture which can produce coronary (sub)occlusion by coronary thrombosis, spasm, or both.

Key words: Coronary syndrome; Exercise testing; Coronary angiography

Introduction

The occurrence of unstable angina, acute myocardial infarction and sudden death after a normal exercise stress test is rare [1–8]. The mechanism(s) responsible for these events is/are still uncertain [9]. Coronary angiographic studies of acute coronary syndromes precipitated by exercise are still lacking. We report the clinical and acute coronary angiographic findings of seven patients with either unstable angina or acute myocardial infarction and after resuscitation from sudden death which occurred after an exercise stress test. These findings can help in gaining a better insight into the pathophysiology of coronary events related to exercise.

Materials and Methods

In the period between March 1984 and September 1988, seven patients developed a coronary event after an exercise stress test. The test was normal in six and positive in one. Coronary angio-

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graphy was previously performed in four patients. In view of the unexpected development of acute ischemic cardiac manifestations after the exercise test, coronary angiography was acutely performed.

Maximal exercise tolerance was performed on a bicycle ergometer according to a modified Bruce protocol [10] having as end-points exhaustion, anginal pain or myocardial ischemia on the electrocardiogram. A 12-lead electrocardiogram was recorded during and up to four minutes after exercise. The blood pressure was recorded before the test and at maximal exercise tolerance. The exercise test was defined as abnormal (or positive) if the patient developed anginal symptoms and/or ≥ 1 mm ischemic ST-segment changes.

Unstable angina was diagnosed in the case of chest pain and typical signs of myocardial ischemia on the electrocardiogram which were relieved by the administration of sublingual or intravenous nitroglycerin. The diagnosis of acute myocardial infarction was made when continuous chest pain was present, with typical electrocardiographic signs of myocardial ischemia unrelieved by nitroglycerin administration. Sudden death was defined as natural unexpected witnessed death, heralded by abrupt loss of vital signs, which occurred with or without preceding cardiac symptoms.

All patients received intravenous nitroglycerin (15 μg/min), heparin (5000 U) and aspirin (500 mg) prior to coronary angiography.

At the investigator's discretion coronary angiography was preceded by the infusion of 1.5×10^6 IU of streptokinase over 30 minutes in order to reduce treatment delay. Coronary angiography was performed via the femoral approach using standard catheters. If the ischemia-related coronary artery was occluded 200 μg nitroglycerin was administered intracoronary, followed by a repeat angiogram. If occlusion was not relieved 250 000 IU of streptokinase was infused intracoronary over 50 minutes in order to achieve reperfusion. Mechanical reperfusion was attempted in case of failure of streptokinase therapy.

The presence of coronary spasm was indicated by the opening of a previously occluded coronary artery after administration of intracoronary nitroglycerin [11]. Intracoronary thrombi were identified as spherical, ovoid or irregular filling defects outlined by contrast medium [12]. The morphology of coronary artery lesion was described according to the classification of Ambrose et al. [13] as either concentric or eccentric with regular (type I) or irregular (type II) border. The electrocardiograms and coronary angiograms were independently reviewed by three experienced cardiologists.

Patients

The clinical characteristics of the patients are listed in Table 1. There were five males and two females with a mean age of 49.8 years (range 37–66). Four patients smoked. None of the patients had elevated blood lipid levels, hypertension or a family history of coronary arterial disease. Three patients exercised regularly and participated

TABLE 1

Clinical characteristics of patients with a coronary event after an exercise stress test.

Patient No.	Sex	Age (yr)	Smoker	Sport	Previous infarction	Exercise test	Time to symptoms (min)
1	M	43	No	Yes	No	Normal	110
2	M	45	Yes	No	No	Positive	10
3	M	41	Yes	No	Yes L	Normal	45
4	F	63	No	No	No	Normal	3
5	F	54	No	Yes	No	Normal	30
6	M	37	Yes	Yes	Yes I	Normal	60
7	M	66	Yes	No	Yes I	Normal	10

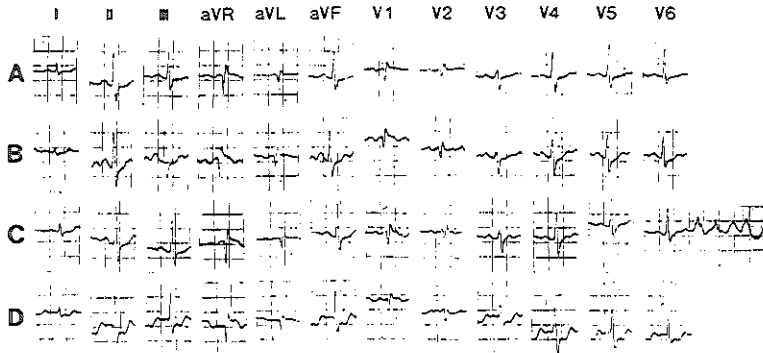M = male; F-female; yr = years; L = lateral; I = inferior.

Fig. 1. Patient 4. (A) Twelve-lead electrocardiogram before the exercise test. (B) At maximal exercise tolerance. (C) After exercise, during the third minute of recovery, showing initiation of ventricular tachycardia. (D) After spontaneous termination of the tachycardia showing ST-segment depression in leads II, III and aVF and V3 to V6.

in amateur sporting competitions. Three patients had had a small myocardial infarction. The exercise stress test was normal in all but one. The patients developed symptoms within a mean of 38 minutes (range 3–110) after the end of the test. A short description of every patient follows.

Patient 1. A 43-year-old man was referred for a screening exercise stress test. Although he spent about 10 hours a week in sporting activities without complaints, he sometimes experienced a slight oppressive feeling on the chest on exertion. He had a normal test and reached 120% of the normal maximal exercise tolerance. About 1 hour and 50 minutes after the test he suddenly developed chest pain, radiating to his left arm and jaws. He immediately returned to the hospital, where a repeat electrocardiogram showed $2\frac{1}{2}$ mm ST-segment elevation in leads II, III, and aVF. After failure of sublingual and intravenous nitroglycerin, pain was relieved and the electrocardiogram normalised after intravenous streptokinase.

Patient 2. A 45-year-old man was admitted because of suspicion of unstable angina without electrocardiographic abnormalities. A coronary angiogram revealed a 50% stenosis in the right coronary artery. An exercise test was performed six days later. He had a normal exercise tolerance,

but he developed slight chest pain and $1\frac{1}{2}$ mm ST-segment depressions in V1 to V3. During the recovery period the electrocardiogram normalised and the pain was relieved. Ten minutes after the test he developed chest pain again. An electrocardiogram showed 3 mm ST-segment elevation in leads II, III and aVF, unrelieved by nitroglycerin administration.

Patient 3. A 41-year-old man was admitted with a lateral myocardial infarction. Acute coronary angiography revealed occlusion of a large obtuse marginal branch and a 55% stenosis of the right coronary artery. The occlusion was relieved after administration of intracoronary streptokinase. He developed a non-Q wave lateral myocardial infarction and remained asymptomatic. Two months later an exercise stress test was performed to assess his cardiac state. He had a normal maximal exercise tolerance.

Forty-five minutes after the test he suddenly developed chest pain and directly came back to the hospital, where an electrocardiogram showed 3 mm ST-segment elevation in leads II, III and aVF. The pain was not relieved by oral and intravenous nitroglycerin.

Patient 4. A 63-year-old female was referred because of palpitations without syncope, unrelated

to exercise. Although she had no anginal complaints, a routine exercise stress test was performed. Her exercise tolerance was 90% of the expected value. The test was normal but during the third minute of recovery she suddenly developed ventricular tachycardia (Fig. 1) and fainted. The tachycardia terminated spontaneously after 70 seconds, just before a precordial electric shock was given. Directly after the electrocardiogram showed 2 mm ST-segment depression in leads II, III, aVF and V3 to V6. The patient recovered at once but about 1 minute later complained of chest pain. Electrocardiographic changes and pain were relieved after administration of intravenous nitroglycerin.

Patient 5. A 54-year-old physically active female underwent an exercise stress test for a periodical sport screening. She had no anginal complaints. She had a normal exercise test and achieved 150% of her expected maximal exercise tolerance. Thirty minutes after the test she complained of sudden chest pain. A general practitioner suspected acute myocardial infarction and called for an ambulance. Before the ambulance arrived she collapsed and cardiopulmonary resuscitation was started directly. The ambulance personnel registered ventricular fibrillation and she was promptly defibrillated. In the hospital an electrocardiogram showed 4 mm ST-segment elevation in V2 to V6.

Patient 6. This case was the subject of a previous report in this journal [8]. In brief, a 37-year-old male, who was admitted with a small inferior myocardial infarction, one month later, an hour after a normal exercise stress test, developed an anterior myocardial infarction with occlusion of a previously angiographically normal left anterior descending artery.

Patient 7. A 66-year-old man was admitted with an acute inferior myocardial infarction and was treated with thrombolytic therapy. He developed a non-Q wave infarction. Although he remained asymptomatic, coronary angiography performed ten days after admission showed a 60% stenosis in the middle traject of a large right coronary artery. Three weeks later an exercise stress test was performed. He reached 80% of the expected maximal exercise tolerance. The test was normal, but ten minutes later he complained of sudden chest pain. An electrocardiogram showed 2 mm ST-segment depression in leads II, III and aVF and V4 to V6. Pain and electrocardiographic changes were relieved after intravenous nitroglycerin.

Results

The angiographic findings of the patients are listed in Table 2. After the exercise test four

TABLE 2

Coronary angiographic findings of patients with a coronary event after an exercise stress test.

Case no.	Clinical presentation	Time to CAG (min)	Coronary artery		Reperfusion	Morphology of lesion	Thrombus
			Prior to test	After test			
1	AMI	80	?	RCA 90%	After SK i.v.	ER	No
2	AMI	50	RCA 50%	RCA 100%	Yes, SK i.c.	EI	Yes
3	AMI	50	RCA 55%	RCA 100%	Yes, NTG i.c.	EI	Yes
4	UA	60	?	IM 90%		ER	No
5	SD	90	?	LAD 100%	No	?	?
6	AMI	95	LAD 0%	LAD 100%	Yes, NTG i.c.	EI	Yes
7	UA	45	RCA 60%	RCA 95%		ER	No

AMI = acute myocardial infarction; UA = unstable angina; SD = sudden death; RCA = right coronary artery; LAD = left anterior descending artery; IM = intermediate artery; % = per cent of stenosis; CAG = coronary angiography; SK = streptokinase; i.v. = intravenous; i.c. = intracoronary; NTG = nitroglycerin; ER = eccentric regular; EI = eccentric irregular.

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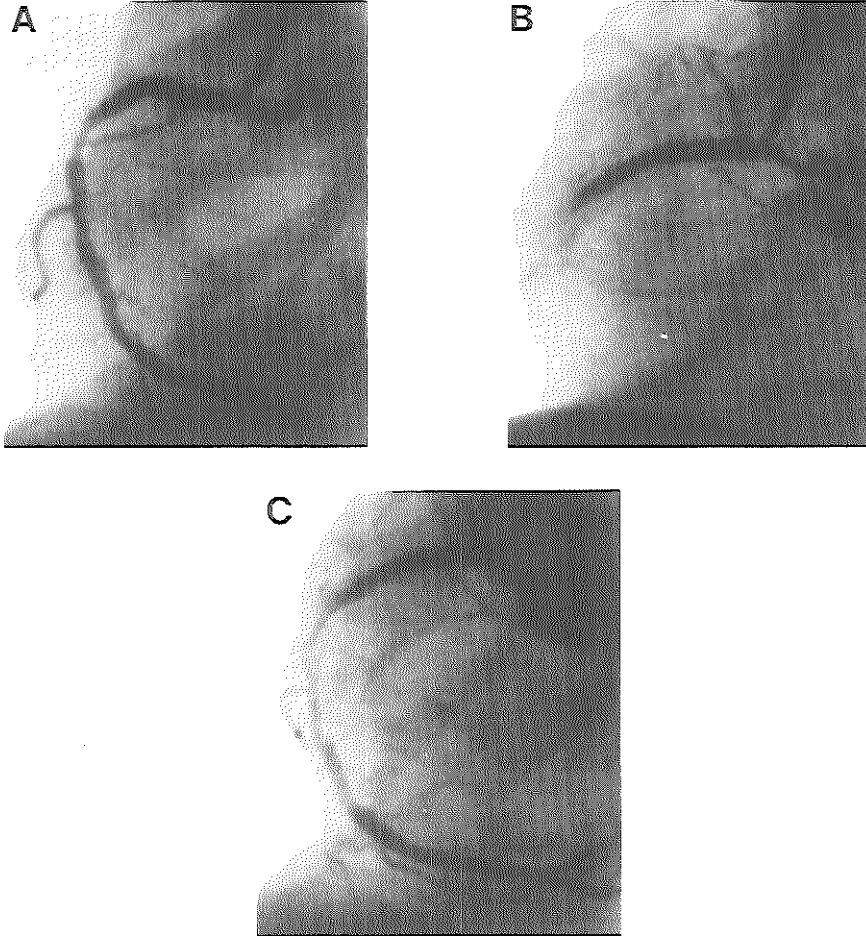
Fig. 2. Patient 3. (A) Right coronary angiogram showing a moderate proximal stenosis. (B) Two months later, 95 minutes after a normal exercise test, showing proximal occlusion. (C) Reperfusion is achieved after 200 μg nitroglycerin intracoronary; an eccentric irregular lesion and intracoronary thrombi are visible at the site of previous occlusion.

patients developed an acute myocardial infarction, two patients developed unstable angina and one was admitted after being resuscitated from sudden death. The mean time between the onset of symptoms and the performance of coronary angiography was 67 minutes (range 45–95).

The ischemic localisation on the electrocardiogram after the exercise test corresponded in all cases with the ischemia-related coronary artery. At coronary angiography four vessels were occluded: in three cases of acute myocardial infarction and in the case of sudden death. The remaining three

vessels, including one after intravenous streptokinase therapy, were patent and showed severe obstruction. Reperfusion resulted in two of the four occluded vessels after intracoronary administration of nitroglycerin (Fig. 2) and in one after intracoronary streptokinase. One vessel remained occluded in spite of all attempts to achieve reperfusion. Coronary morphology was determined in six vessels with less than 100% obstruction either directly or after reperfusion. In all vessels an eccentric lesion was present, in three with regular (type I) and in three with irregular (type II) borders (Fig. 2). Intracoronary thrombus was visualised in three vessels after reperfusion either with streptokinase or nitroglycerin (Fig. 2). In four cases previous coronary angiographic study showed no evident or moderate obstructive disease of the vessel which was involved in the coronary event after the exercise test (Fig. 2). The percentage of increase of lumen obstruction of these four vessels after the exercise test varied from 35 to 100%.

Discussion

The occurrence of acute myocardial infarction and sudden death in relation to exercise stress testing has been reported in the literature in only a few cases [1–8]. An extensive survey of 518 448 exercise tests has shown a myocardial infarction rate of 3.58 and a mortality rate of 0.5 per 10 000 tests [14]. Nevertheless, the development of an acute coronary event in association with a normal exercise test is still rare [1,4,5,7,8].

The pathophysiology of a coronary syndrome after normal responses to an exercise stress test and without electrocardiographic evidence of myocardial ischemia is still hypothetical. In one case of acute myocardial infarction after a normal exercise test coronary thrombosis was indicated as being responsible for the asymptomatic occlusion of a right coronary artery [7]. It has been demonstrated by Davies, Thomas and Falk that coronary thrombosis is almost exclusively the result of an acutely damaged intima [15,16]. These authors showed that plaque fissuring or rupture represents the pathological substrate of acute and sub-acute coronary (sub)occlusion. The occurrence of rupture of an atheromatous plaque can lead to a series of dynamic intracoronary changes resulting in thrombosis, intimal haemorrhage, thromboembolisation and spasm, thereby creating the conditions for coronary (sub)total occlusion.

The present report has shown that unstable angina, acute myocardial infarction and sudden death can develop after normal and positive exercise stress testing. Acute coronary angiographic study showed in three cases coronary occlusion which was due to thrombosis, spasm or both. In one case vessel patency after intravenous streptokinase suggested prior thrombosis. In two other cases the presence of coronary spasm was indirectly demonstrated by the relief of chest pain and normalisation of the electrocardiogram after intravenous nitroglycerin. Persistence of vessel occlusion after intravenous and intracoronary nitroglycerin excluded the presence of spasm as an aetiological factor in these patients. The morphology of the coronary lesions was eccentric in all cases, either with regular (type I) or irregular (type II) borders. These lesions have been correlated at necropsy and in clinical angiographic studies with ruptured plaques, with or without intraluminal thrombosis [13,17]. Furthermore, in four patients (patients 2, 3, 6, 7) coronary angiography was previously performed and showed no evident or moderate obstructive disease of the vessel which was involved in the coronary event after the exercise test. In these four vessels the increase in stenosis up to complete occlusion after the exercise test was related to coronary spasm, thrombosis or both, and was associated with an eccentric lesion consistent with plaque rupture. These cases are in accordance with the necropsy findings of Davies and Thomas [15] that rupture, leading to (sub)total coronary occlusion, can occur in plaques which involve 50% or less of the vessel diameter.

It has been stated that the electrocardiogram can fail to detect myocardial ischemia during exercise [10].

This report clearly demonstrates that the electrocardiogram did not show myocardial ischemia during exercise, doubtless because ischemia was not present. At the very moment the patients developed symptoms, typical signs of myocardial ischemia were also detected on the electrocardio-

gram. Consequently, the sudden onset of symptoms implies a sudden sub-total or total impairment of coronary flow. The latter can, in turn, be the result of an equally sudden change or the culmination of changes initiated during exercise in the coronary artery involved. It can therefore be hypothesised that in our patients during exercise an acute intimal change occurred which led to the manifestation of a coronary event after exercise. The trigger responsible for such an acute intimal change during exercise could be vasospasm.

Active vasospasm has been observed during exercise in patients with variant and classic angina [11,18,19] and is probably related to unopposed α-adrenergic stimulation by circulating catecholamines due to abnormal endothelial reactivity of the diseased segment of the coronary artery [20,21]. We suggest that in our patients active repeated vasospasm during the exercise test could have induced fissuring or rupture of a plaque which led to coronary (sub)occlusion after exercise. The dynamic changes evoked by plaque rupture can evolve over a relatively long period of time before coronary (sub)occlusion occurs [22]. In a previous coronary angiographic study we proposed that plaque rupture could be the precipitating factor of acute myocardial infarction and sudden death after sporting activities [23]. The development of a large intimal hemorrhage as a consequence of plaque rupture can also explain the failure of reperfusion measures in one of our patients [15,24].

In addition, the course of patient 2 indicates that clinical judgement remains of major importance in spite of reassuring coronary angiographic findings. In the case of unstable angina an exercise test is avoided in order to prevent unnecessary deleterious consequences for the patient [3,6]. An "unstable" coronary lesion or a damaged intima (i.e. after coronary angioplasty) can abnormally react to the physiologic changes evoked by exercise which are potentially capable of producing coronary occlusion [2,6,10,21,25,26].

It is also noteworthy that in patient 4 ventricular tachycardia ensued before myocardial ischemia was symptomatic or registered on the electrocardiogram (Fig. 3). This case of "aborted" sudden death shows that the first manifestation of sudden ischemia can be a life-threatening arrhythmia and suggests a similar sequence for the occurrence of sudden death related to exercise in people without previous symptoms.

In conclusion, our findings show that unstable angina, acute myocardial infarction and sudden death can occur unexpectedly after a normal exercise test in patients with previous moderate or even no evident obstructive coronary artery disease. The underlying mechanism is most probably related to exercise-induced plaque rupture which can produce coronary (sub)occlusion by coronary thrombosis, spasm, or both. A similar mechanism may be responsible for the acute coronary events related to sport in previously asymptomatic people.

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Exercise-induced plaque rupture producing myocardial infarction

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A 37-year-old man with unstable angina was subjected to coronary angiography. The right coronary artery showed a minor proximal stenosis, but there were no obstructive lesions in the left coronary artery. He developed a small inferior infarction. He was asymptomatic until re-admission 1 month later, 1 hour after a normal exercise test, with anterior myocardial infarction. Acute coronary angiography showed sub-total occlusion of the left anterior descending artery. The occlusion was partially relieved after intracoronary injection of nitroglycerin. Intracoronary infusion of streptokinase had no further effect. Balloon angioplasty was then successfully performed. It is suggested that stress-induced plaque rupture with intimal hemorrhage and secondary spasm resulted in sub-total occlusion of the left anterior descending artery producing the second myocardial infarction.

(Key words: plaque rupture; exercise; myocardial infarction)

Introduction

The pathophysiology of exercise-related myocardial infarction and sudden cardiac death is still uncertain. We report the case of a patient with recurrent infarction in whom the second

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episode, 1 hour after a normal exercise test, was associated with sub-total occlusion and vasospasm of a previously angiographically normal coronary artery. Our observations of this exceptional case suggest that exercise-induced plaque rupture can lead to the development of myocardial infarction. This report may help in the understanding of the mechanism(s) by which physical exercise can precipitate infarction.

Case Report

A 37-year-old man was admitted to the coronary care unit on 4 February 1984, with chest pain of 2 hours duration. He smoked 20 cigarettes daily but there were no other risk factors. On examination the venous pressure was normal, the pulse regular 75/min and the blood pressure 130/80 mm Hg. The rest of the physical examination was not informative. The chest X-ray examination was normal. The electrocardiogram showed inferior ischemia (Fig. 1A).
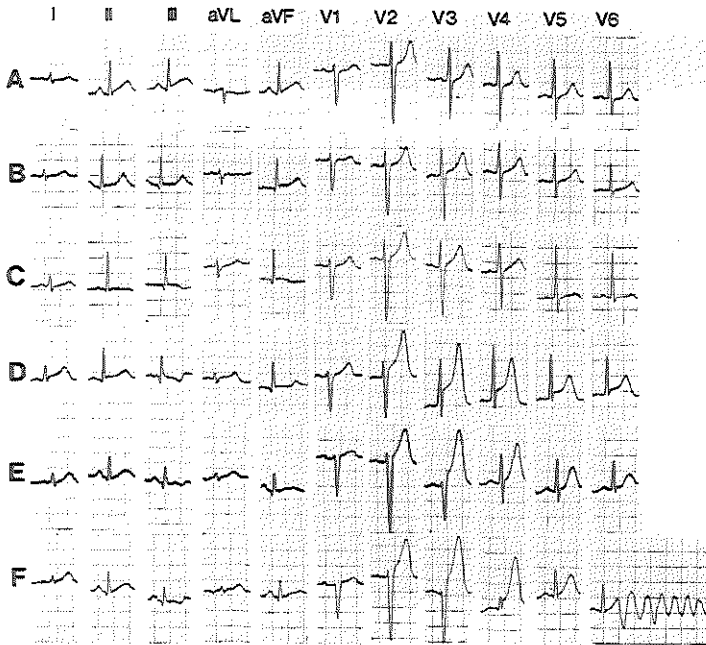
Fig. 1. ECG on first admission showing slight ST-elevation in leads II, III and aVF (A); normalisation after 0.5 nitroglycerin sublingually (B); inverted T-waves in II, III and aVF 1 day later compatible with a limited inferior myocardial lesion (C). ECG on second admission, 1.5 hours after a normal exercise test showing ST-elevation in I, II, aVL and V2 to V6 (D); reduction of ST-elevation after nifedipine 20 mg buccally (E); after a few minutes increase of ST-segment elevation and ventricular fibrillation (F).
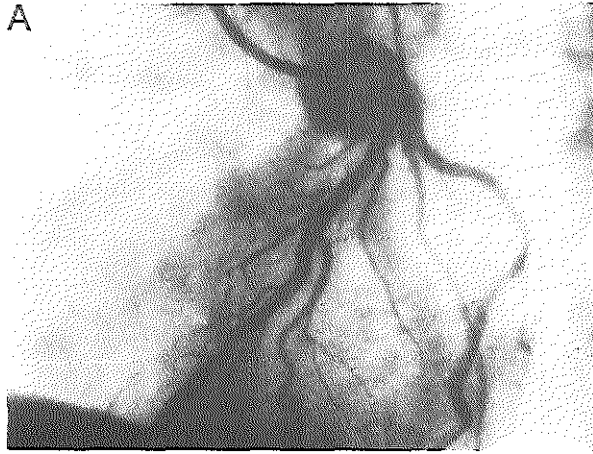
Fig. 2. Left coronary angiogram showing a patent left anterior descending artery (A) and a right coronary with minimal proximal stenosis (B). Left coronary angiogram on second admission, showing an eccentric sub-total proximal occlusion of the left anterior descending artery (C); partial relief of occlusion after 600 μg nitroglycerin intracoronary (D); after angioplasty of the obstructed segment: steerable guide wire still in the left anterior descending artery (E); 3.5 months after angioplasty, showing a minor eccentric lesion at the site of the previous occlusion (F).
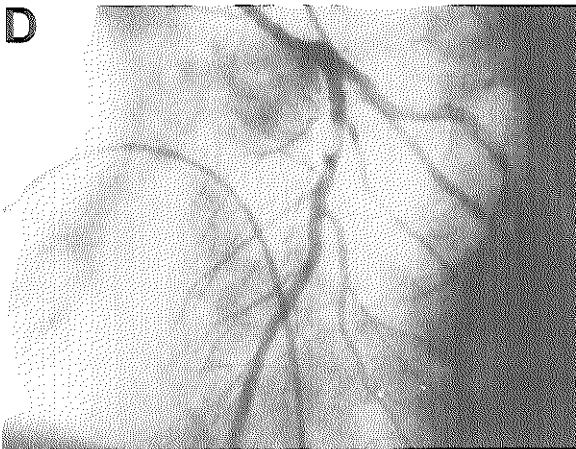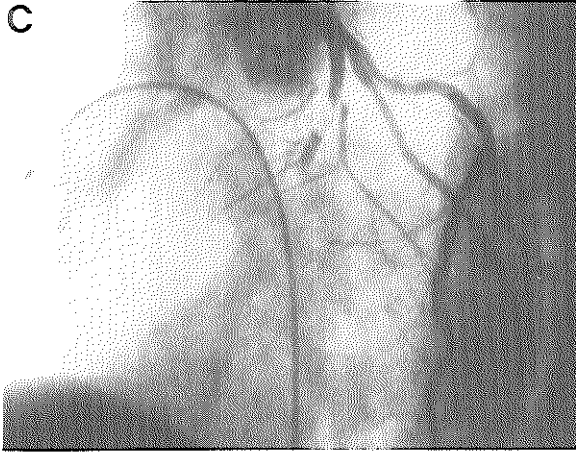
Fig. 2, continued.

Nitroglycerin 0.5 mg sublingually relieved the pain promptly. A second electrocardiogram was normal (Fig. 1B). A diagnosis of unstable angina was made and cardiac catheterisation was performed 1.5 hours after admission. There were no obstructive lesions in the left coronary artery (Fig. 2A). The right coronary artery showed a minor proximal stenosis but no signs of intracoronary embolisation (Fig. 2B). Vasospastic angina was suspected and he was

E

F
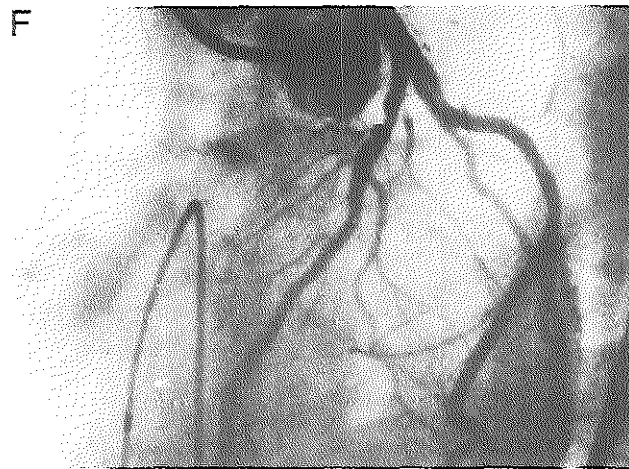
Fig. 2. continued.

treated with nifedipine 40 mg daily. On 5 February a peak serum creatine kinase of 356 U/l (normal up to 120 U/l) and minor electrocardiographic changes (Fig. 1C) were compatible with the diagnosis of a limited inferior myocardial infarction. The patient was mobilised and discharged on therapy with nifedipine. An exercise test was performed on a bicycle ergometer

on 5 March 1984 at 4.00 p.m. He had a normal exercise tolerance (200 watts); maximal heart rate and blood pressure were respectively 170 beats per minute and 200/90 mm Hg. The end-point was exhaustion but he had no anginal complaints. The 12-lead electrocardiogram recorded during and upto 4 minutes after exercise remained normal. At 5.25 p.m. he developed severe chest pain that was not relieved by 1 mg sublingual nitroglycerin. He was admitted at 5.45 p.m. An electrocardiogram showed transmural anterior ischemia (Fig. 1D). Pain was completely relieved after two doses of 10 mg nifedipine were administered sublingually in 5 minutes. Ventricular fibrillation occurred shortly afterwards and he was electrically defibrillated. A subsequent tracing showed reduction of ST-segment elevation (Fig. 1E). An intravenous nitroglycerin infusion 10 μg/min was then begun.

A few minutes later the patient experienced chest pain once again that was not relieved by sublingual nitroglycerin and nifedipine and ventricular fibrillation recurred (Fig. 1F). He was promptly defibrillated. In view of the evolving anterior myocardial infarction, coronary angiography was performed at 7.00 p.m. This showed a sub-total proximal occlusion of the left anterior descending artery with very slow distal filling (Fig. 2C). After intracoronary injection of 600 μg nitroglycerin partial relief of the occlusion occurred with improved flow and complete distal filling of the vessel (Fig. 2D). Streptokinase was then infused into the left coronary artery at a rate of 5.000 U/minute, for 50 minutes, without further relief of the obstruction. Transluminal coronary angioplasty was then successfully performed (Fig. 2E). The patient developed an anterior myocardial infarction. His serum plasminogen activity (96%) and coagulation parameters were normal. A repeat bicycle exercise test on 22 June 1984 was normal. Cardiac catheterisation was performed 0.5 hour after the exercise test. The left ventriculogram showed localised apical akinesia. The ejection fraction was 67%. The left anterior descending artery showed a minor eccentric lesion at the site of the previous occlusion (Fig. 2F). The right coronary lesion was unchanged. The patient is still doing well 23 months following angioplasty.

Discussion

Coronary spasm is present in some cases of myocardial infarction in the early hours [1]. The first infarction in our patient was probably precipitated by vasospasm of the right coronary artery. Prompt relief of pain after administration of nitroglycerin sublingually and the presence of a minor stenosis in the artery support this hypothesis [1]. Plaque rupture with secondary spasm and microscopic coronary embolisation cannot, however, be excluded [2,3]. The second infarction occurred after a normal exercise test. Two case reports [4,5] have already documented the occurrence of infarction shortly after a normal exercise test but in both cases the state of the coronary arteries prior to the infarct was unknown. In our patient there was no angiographic evidence of obstructive lesions in the left coronary artery 1 month before the second infarct. On admission relief of pain after sublingual nifedipine followed by ventricular fibrillation and slight ST-segment changes suggested the presence of spasm. Coronary angiography revealed a subtotal occlusion of the left anterior descending artery. The second coronary angiogram performed after intracoronary administration of nitro-glycerin showed improvement in coronary patency and in forward flow. These changes were consistent with relief of spasm at the site of the occlusion [1]. Administration of intracoronary streptokinase had no further effect on the coronary obstruction. Failure of streptokinase therapy in the presence of normal coagulation parameters and presumably a fresh thrombus is very unusual [5].

Intra-intimal hemorrhage can produce a similar angiographic appearance [2,3] that will not resolve after administering streptokinase. Two possible mechanisms can be implicated in

the occurrence of the second myocardial infarct. (1) Physical exertion precipitated spasm which in turn caused endothelial damage with subsequent platelet aggregation and thrombus formation [1]. Spasm has been described during or shortly after exercise. A delayed onset is unlikely. (2) Exercise precipitated rupture of an atheromatous plaque with intimal haemorrhage which evoked local spasm resulting in sub-total coronary occlusion. Davies and Thomas [2] and Falk [3] have recently demonstrated that almost all infarct related coronary arteries showed fissuring or rupture of atheromatous plaques which can result in intimal hemorrhage, thrombosis, thrombo-embolism or spasm, thereby representing the pathological basis of unstable angina, myocardial infarction and sudden death. The dynamic changes initiated by plaque rupture may have a rapid or relatively long evolution thus explaining the delay between the end of the sporting activity and the onset of symptoms or sudden death.

Our case allows us to conclude that exercise can precipitate myocardial infarction with occlusion of a previously patent coronary artery. Prior angiographic knowledge of the coronary anatomy supported our diagnosis of plaque rupture as the underlying cause.

Acknowledgement

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CHAPTER 5

CLINICAL CHARACTERISTICS AND CORONARY ANGIOGRAPHIC
FINDINGS OF PATIENTS WITH UNSTABLE ANGINA, ACUTE
MYOCARDIAL INFARCTION AND SURVIVORS OF SUDDEN ISCHEMIC
DEATH OCCURRING DURING AND AFTER SPORT

Recurrent acute myocardial infarction during sport

Clinical characteristics and coronary angiographic findings of patients with unstable angina, acute myocardial infarction, and survivors of sudden ischemic death occurring during and after sport

The clinical characteristics and coronary angiographic findings of 42 well-conditioned subjects with an acute ischemic event related to sport are reported. Five patients had unstable angina, 25 had acute myocardial infarction (AMI), and 12 were resuscitated victims of sudden ischemic death. Twenty-two events occurred during sport (group A) and 20 after sport (group B). There were two women and 40 men. The mean age was 46 years (range 25 to 65). Twelve out of 30 patients who smoked cigarettes had an adjunctive risk factor for coronary artery disease. Twelve others (28%) had no identifiable risk factor. Prodromal cardiac symptoms were detected in three patients (group A). Two patients had previous myocardial infarction (group B). Coronary angiography was performed acutely in 39 patients. The distribution of the ischemia-related coronary artery was comparable in both groups. The lesion morphology of 35 culprit coronary arteries was described as concentric in six patients and eccentric with regular borders (type I lesion) in 11 and irregular borders (type II lesion) in 18. Eccentric lesions consistent with ruptured plaques prevailed in both groups. Associated coronary artery disease was present in 10 patients. There was no relationship between the number of risk factors and the extent of diseased coronary arteries. Clinical characteristics and coronary angiographic findings of patients with unstable angina, AMI, and sudden death either during or after sport are similar and indicate a common pathogenesis. The probable mechanism of a coronary event related to sport is exercise-induced plaque rupture. In most instances such an event is unexpected and unpredictable. Identification of some subjects at risk is possible. (Am Heart J 1990;120:1267.)

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Although reports on sudden death in relation to sporting activities are numerous,[1-17] there are no studies that relate the occurrence of unstable angina, acute myocardial infarction (AMI), and sudden death to physical exertion. The current opinion is that in middle-aged people the majority of sudden deaths associated with sport are due to preexistent silent severe coronary artery disease.[5-17] However, since

acute coronary angiographic studies in this setting are lacking and most of our present knowledge is based on necropsy findings, the pathogenesis of acute ischemic syndromes related to sport is still speculative.[1-17]

The purpose of this study was to report the clinical characteristics and acute coronary angiographic findings of well-conditioned, habitually sportive subjects with unstable angina or AMI and those resuscitated from sudden death that occurred during and after sport. Documentation and analysis of these data may establish a direct cause-effect relationship between sport and coronary events and may elucidate the underlying pathogenesis. It was also postulated that, physical exercise being the common denominator, coronary findings and coronary morphologic fea-

Table I. Clinical characteristics of patients with unstable angina, AMI, and sudden death during sport (group A)

No.	Clinical presentation	Sex	Age (yr)	Risk factors	Sport (hr/wk)	Type of sport	Prodromata	Time (min) to symptoms*	Time (min) to sudden death†	Time (min) to CAG†
1	UA	M	56	C, H	5	Cycling	No	40		100
2	UA	M	52	No	6	Ice skating	No	10		120
3	AMI	M	50	No	6	Ice skating	No	30		120
4	AMI	M	41	C, F	4	Soccer	No	60		110
5	AMI	M	33	C	6	Squash	No	30		100
6	AMI	M	45	C, F	4	Hockey	No	25		140
7	AMI	M	31	C	4	Handball	No	20		90
8	AMI	M	45	C	8	Tennis	No	30		90
9	AMI	M	54	C	3	Tennis	No	20		120
10	AMI	M	51	C, Chol	6	Tennis	No	20		120
11	AMI	M	52	No	10	Cycling	No	30		120
12	AMI	M	64	C, H	3	Tennis	No	20		180
13	AMI	M	34	No	7	Soccer	No	20		120
14	AMI	M	52	H	10	Cycling	No	30		90
15	AMI	M	25	No	8	Jogging	No	40		130
16	AMI	M	47	C, Chol	2	Soccer	No	15		‡
17	SD	M	46	C	10	Cycling	No	40	20	80
18	SD	M	48	No	6	Soccer	No	20	0	60
19	SD	M	45	C	3	Volleyball	No	30	0	80
20	SD	M	39	No	6	Tennis	No	30	0	100
21	SD	M	49	No	4	Tennis	No	45	0	‡
22	SD	M	55	H	9	Tennis	No	10	0	‡

UA, Unstable angina; SD, sudden death; C, cigarette smoking; H, hypertension; F, family history of coronary artery disease; Chol, high cholesterol level; CAG, coronary angiography.
*After start of sport.
†After onset of symptoms.
‡Coronary angiography delayed.

tures of unstable angina, AMI, and sudden death may be similar. Therefore it was hypothesized that the underlying mechanism was probably the same.[18] In addition, it may be possible to detect markers that identify subjects at risk for a coronary event related to physical exertion.

METHODS

Patients. During the period between July 1984 and March 1989, a total of 42 consecutive subjects—well-trained, conditioned sportsmen and women—were admitted to our three institutions with a diagnosis of unstable angina or AMI or as resuscitated victims of sudden death that occurred in relation to sporting activities. All of these previously healthy subjects, most of whom were members of veterans' sports clubs, had exercised regularly since their youth (10 to 45 years), and although they were not athletes or professionals, most of them participated at least once a month in veteran sporting competitions. The sporting activities included cycling, ice skating, soccer, squash, handball, tennis, jogging, volleyball, hockey, and badminton (Tables I and II). Besides their regular sporting and competitive activities, they also enjoyed leisure-time physical exercise and 40% were employed in jobs that required heavy physical exertion.

Clinical definitions. A coronary event was considered to be related to physical exertion if it occurred during exercise or within the first hour thereafter.[20] Unstable angina was diagnosed in the case of intermittent chest pain and typical ECG changes (defined as ST segment elevation or depression, negative T waves in two or more leads, or both), which were at least temporarily relieved by the administration of sublingual or intravenous nitroglycerin and were not associated with any increase in serum enzyme levels. AMI was diagnosed when continuous chest pain, lasting longer than 30 minutes, was associated with 2 mm ST segment elevation and/or depression in two or more contiguous leads,[19] unrelieved by sublingual and intravenous administration of nitroglycerin, together with an increase in serum glutamic oxaloacetic transaminase and/or serum creatine phosphokinase and creatine kinase MB fractions. Sudden death was defined as unexpected natural witnessed death, heralded by the abrupt loss of vital signs, which occurred either with or without preceding symptoms during exercise or within the first hour thereafter.[20]

Eligibility for the study. Patients with unstable angina and AMI were eligible for the study if they were admitted within 3 hours after the onset of symptoms. Survivors of sudden death were eligible if (1) cardiopulmonary resuscitation was initiated immediately after the onset of sudden death and did not last longer than 20 minutes; (2) the ECG after resuscitation showed acute transmural ischemia; (3)

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Table II. Clinical characteristics of patients with unstable angina, AMI, and sudden death after sport (group B)

No.	Clinical presentation	Sex	Age (yr)	Risk factors	Sport (hr/wk)	Type of sport	Prodromata	Time (min) to symptoms*	Time to sudden death†	Time (min) to CAG†
1	UA	M	49	C	4	Badminton	No	15		90
2	UA	M	40	C	6	Tennis	Yes	15		120
3	UA	M	49	C	4	Badminton	No	15		80
4	AMI	M	42	C, F	4	Jogging	No	60		165
5	AMI	M	40	C	4	Cycling	No	45		60
6	AMI	M	65	No	15	Cycling	No	20		80
7	AMI	M	47	C, F	3	Cycling	Yes	60		145
8	AMI	F	42	C, F	2	Volleyball	No	20		170
9	AMI	M	48	C, F	3	Soccer	No	10		60
10	AMI	M	49	C, H	4	Tennis	No	60		200
11	AMI	M	52	No	10	Jogging	No	15		120
12	AMI	M	51	No	7	Jogging	No	15		180
13	AMI	M	39	C, F	6	Soccer	No	30		200
14	AMI	M	46	C	5	Soccer	No	10		140
15	SD	M	49	C	7	Cycling	No	10	15	70
16	SD	M	37	C	3	Soccer	No	45	0	90
17	SD	M	34	No	10	Soccer	No	30	0	60
18	SD	M	37	C	3	Cycling	No	45	15	95
19	SD	M	59	C	8	Cycling	Yes	20	0	90
20	SD	F	55	C	4	Cycling	No	30	15	100

UA, Unstable angina; SD, sudden death; C, cigarette smoking; H, hypertension; F, family history of coronary artery disease; CAG, coronary angiography.
*After the end of sport.
†After onset of symptoms.

the time between the onset of symptoms or sudden death and admission was not longer than 3 hours, (4) the patient remained in a stable hemodynamic condition without recurrent life-threatening rhythm disturbances, and (5) on physical and chest x-ray examination there were no detectable traumatic complications related to cardiopulmonary resuscitation. The all-group exclusion criteria were (1) age over 70 years, (2) previous treatment with streptokinase, (3) enhanced risk of bleeding, (4) pregnancy, and (5) recent cerebrovascular accident. Informed consent was obtained from the patients or their relatives.

Procedure and angiographic definitions. A single-lead ECG registration was made by ambulance personnel in all victims of sudden death at the time of cardiopulmonary resuscitation. Coronary angiography was performed in all instances. At the beginning of the study patients underwent acute coronary angiography. At a later stage coronary angiography was delayed (within 1 week) in those patients in whom there was a definitive resolution of symptoms and/or ischemia shortly (within 30 minutes) after therapeutic measures were begun (see below). All patients received intravenous nitroglycerin (15 µg/kg/min.), heparin (5000 U), aspirin (250 mg), and dexamethasone (12 mg) before coronary angiography. The ECG was repeated after 5 minutes. If transmural myocardial ischemia persisted, at the investigator's discretion coronary angiography was preceded by the infusion of 1.5×10^6 U of streptokinase over 30 minutes to reduce treatment delay. Prolonged cardiopulmonary resuscitation did not constitute a contraindication for administration of streptokinase.[21, 22] The angiographic anterograde coronary flow through the

obstruction was assessed by means of the grading system of the Thrombolysis in Myocardial Infarction (TIMI) trial[23] (grade 0, no anterograde flow; grade I, penetration of contrast medium beyond the obstruction without distal flow; grade II, slow anterograde flow with distal visualization of the coronary artery; grade III, normal flow.) Coronary arteries showing anterograde flow grades 0 and I were considered to be occluded.

At angiography if the ischemia-related coronary artery appeared to be occluded, 200 µg of nitroglycerin was administered intracoronarily, after which coronary angiography was repeated. Intracoronary infusion of streptokinase was then started at a rate of 5000 U/min until a total dose of 250,000 U was given. Mechanical reperfusion and balloon angioplasty were immediately attempted at the investigator's discretion in case of coronary occlusion or after failure of intracoronary streptokinase therapy.

The presence of coronary spasm[24] was deduced after intracoronary administration of nitroglycerin resulted in opening of a previously occluded coronary artery (i.e., from TIMI grades 0 and I to III). Intracoronary filling defects were defined as being consistent with thrombus if they appeared spherical, ovoid, or irregular outlined by contrast medium.[25] According to the classification of Ambrose et al.,[26] the morphology of coronary artery lesions was described as either concentric or eccentric with regular (type I) or irregular (type II) borders. Eccentric lesions were considered to be consistent with ruptured plaques with or without thrombosis.

Quantitative determination of residual stenosis after reperfusion was performed by measuring the stenotic seg-

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ment and comparing it with an adjacent normal segment proximal and distal to the lesion on an end-diastolic frame in at least two different angiographic projections.

All ECGs and coronary angiograms were reviewed independently by three experienced cardiologists. Laboratory determinations of hemoglobin, renal and liver function, electrolytes, platelet count, fibrinogen and prothrombin time, and cholesterol and triglyceride levels were performed twice in all patients. Before discharge all patients answered a questionnaire concerning symptoms before their cardiac event.[14, 27, 28]

RESULTS

The 42 patients studied were divided into two groups depending on whether their events occurred during (group A) or after (group B) sport. Their clinical characteristics are listed in Tables I and II, respectively. There were 22 events during sport: two patients with unstable angina, 14 with AMI, and six survivors of sudden death. There were 20 events after sport: three patients with unstable angina, 11 with AMI, and six survivors of sudden death. The mean age of group A was 46 years (range 25 to 64) and of group B 46.5 years (range 34 to 65). Two of the 42 patients were women.

Coronary risk factors. Twenty-nine patients (69%) smoked cigarettes (10 to 30/day). Four patients (9.5%) had a history of mild untreated hypertension. Seven patients (16.6%) had a family history of coronary artery disease. Only two patients (4.7%) had elevated cholesterol levels. Twelve patients (28.5%) had no identifiable risk factors for coronary artery disease; 18 (42.8%) had one, and 12 (28.5%) had two.

There was a similar distribution of risk factors in both groups (20 in group A, 22 in group B). There was no significant difference between the two groups with respect to specific risk factors. Coagulation parameters and results of other laboratory investigations were normal in all patients.

Sport-related events. The mean duration of sporting activities per week was 5.9 hours for group A and 5.6 hours for group B. The mean interval between starting sporting activities and the onset of symptoms (group A) was 27.9 minutes. The mean time between the end of sport and the onset of symptoms (group B) was 28.5 minutes. Eight of the 12 victims of sudden death collapsed suddenly without previous symptoms. The remaining four collapsed within 20 minutes after the onset of symptoms. Before resuscitation asystole was monitored in one and ventricular fibrillation in 10 victims of sudden death. In a single patient (No. 20 in group A), no arrhythmia was registered. This patient regained consciousness after 4 to 5 minutes of cardiopulmonary resuscitation before the arrival of the ambulance.

Prodromal symptoms suggestive of anginal complaints were detected in only three patients. Between the two groups there was an equal distribution of events that occurred with almost equal frequency in the morning and in the afternoon. Most sudden deaths, however, occurred in the afternoon (8 out 12). All patients participated in sport at a usual predetermined time of day.

Coronary angiography. The mean total time between the onset of symptoms and acute coronary angiography was similar for both groups (107 minutes in group A; 115 minutes in group B). Coronary angiography was delayed in three patients in whom symptoms and/or ECG signs of ischemia disappeared shortly after administration of nitroglycerin or intravenous streptokinase.

The coronary angiographic findings of group A are listed in Table III and those of group B in Table IV. The ischemic localization on the ECG corresponded in all but one patient (no. 15 in group A) with obstruction or occlusion of the expected ischemia-related coronary artery. In two patients (Nos. 5 and 19 in group B) the ECG showed small Q waves indicating, respectively, an old lateral and an inferior infarction. The left anterior descending artery was involved in 21 patients, the right coronary artery in 15, and the circumflex or obtuse marginal branch in six. The distribution of the culprit coronary artery was comparable in both groups. The left anterior descending artery was the vessel more often involved and significantly so in victims of sudden death as a whole (8 out of 12 patients). The ischemia-related coronary artery was patent but severely obstructed in the five patients with unstable angina.

Reperfusion measures. In AMI and sudden death as a whole, 22 vessels without prior thrombolytic intervention were occluded and four were patent. The remaining 11 vessels were patent after intravenous administration of streptokinase. Reperfusion resulted after intracoronary administration of nitroglycerin in five previously occluded vessels: three of sudden death and two of AMI (Fig. 1). Reperfusion was achieved in 12 other occluded vessels after intracoronary administration of streptokinase.

Mechanical reperfusion and coronary angioplasty were performed in two vessels. Two other vessels remained occluded despite attempted reperfusion. In a single patient in whom ischemia was relieved after intravenous administration of nitroglycerin, the vessel was occluded but filled through collaterals (No. 22 in group A).

Coronary stenosis. Determination of the degree of stenosis of 37 patent and (nonmechanically) reperfused culprit coronary arteries showed an obstruction

Table III. Coronary angiographic findings of patients with unstable angina, AMI, and sudden death during sport (group A)

No.	Clinical presentation	CCA	Patent	Streptokinase	Reperfusion	Stenosis (%)	Morphology of lesion	Thrombus	ACD
1	UA	LAD	Yes	No		95	ER	No	No
2	UA	Cx	Yes	No		99	C.	No	No
3	AMI	LAD	No	Intracoronary	No	100*			No
4	AMI	RCA	No	Intracoronary	Yes	75	EI	Yes	No
5	AMI	LAD	No	Intracoronary	Yes	85	ER	No	No
6	AMI	LAD	No	Intracoronary	Yes	90	EI	No	No
7	AMI	RCA	No	No	Yes, intracoronary NTG	45	ER	No	No
8	AMI	RCA	No	Intracoronary	Yes	30	EI	Yes	No
9	AMI	RCA	Yes	Intravenous		95	C	No	No
10	AMI	LAD	No	Intracoronary	Yes	90	EI	Yes	RCA 70% Cx 75%
11	AMI	LAD	No	Intracoronary	Yes	75	EI	Yes	No
12	AMI	RCA	Yes	Intravenous		90	EI	Yes	No
13	AMI	LAD	Yes	Intravenous		99	EI	No	No
14	AMI	LAD	No	Intracoronary	Yes	85	ER	No	No
15	AMI	RCA	Yes	Intravenous		0			No
16	AMI	LAD	Yes	Intravenous		20	†	No	No
17	SD	RCA	No	No	Yes, intracoronary NTG	95	EI	Yes	No
18	SD	Cx	No	Intracoronary	Yes	95	C	No	LAD 50%
19	SD	LAD	No	Intracoronary	Yes	60	ER	Yes	No
20	SD	RCA	Yes	No		95	EI	Yes	No
21	SD	LAD	Yes	Intravenous		40	ER	No	No
22	SD	LAD	No	No	No	100*			No

UA, Unstable angina; SD, sudden death; CCA, culprit coronary artery; ACD, associated coronary disease; LAD, Left anterior descending artery; RCA, right coronary artery; Cx, circumflex artery; NTG, nitroglycerin; EI, eccentric irregular; ER, eccentric regular; C, concentric.
*Filled by collaterals.
†Contrast medium filling a small wall ulceration.

Table IV. Coronary angiographic findings of patients with unstable angina, AMI, and sudden death after sport (group B)

No.	Clinical presentation	CCA	Patent	Streptokinase	Reperfusion	Stenosis (%)	Morphology of lesion	Thrombus	ACD
1	UA	RCA	Yes	No		85	ER	No	LAD 70%
2	UA	RCA	Yes	No		75	ER	No	No
3	UA	RCA	Yes	No		90	EI	No	LAD 75%
4	AMI	LAD	Yes	No		99	EI	Yes	No
5	AMI	RCA	No	No	Yes, intracoronary NTG	50	EI	Yes	MO 100%*
6	AMI	OM	No	Intracoronary	Yes, mechanical	30†	?	?	RCA 50%
7	AMI	RCA	Yes	No		95	EI	Yes	No
8	AMI	LAD	No	Intravenous	Yes, mechanical	30†	?	?	No
9	AMI	RCA	Yes	Intravenous		80	EI	No	No
10	AMI	OM	Yes	No		95	EI	No	No
11	AMI	LAD	Yes	Intravenous		60	ER	No	No
12	AMI	LAD	Yes	Intravenous		90	ER	No	No
13	AMI	Cx	Yes	Intravenous		95	ER	No	No
14	AMI	RCA	Yes	Intravenous		85	C	No	LAD 40%
15	SD	LAD	No	Intracoronary	Yes	60	EI	No	No
16	SD	LAD	No	Intracoronary	Yes	65	C	No	No
17	SD	Cx	No	Intracoronary	Yes	95	C	No	No
18	SD	LAD	No	No	Yes, intracoronary NTG	90	EI	Yes	RCA 30%
19	SD	LAD	No	No	Yes, intracoronary NTG	85	EI	No	RCA 100%*
20	SD	LAD	No	Intracoronary	No	100*			RCA 40%

UA, Unstable angina; SD, sudden death; CCA, culprit coronary artery; ACD, associated coronary disease; LAD, left anterior descending artery RCA, right coronary artery; Cx, circumflex artery; OM, obtuse marginal; NTG, nitroglycerin; EI, eccentric irregular; ER, eccentric regular; C, concentric.
*Filled by collaterals.
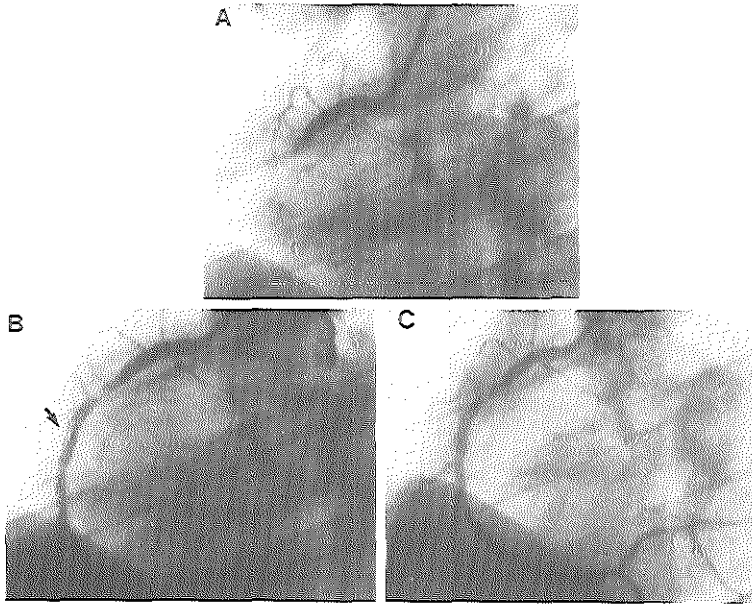†After coronary angioplasty.

Fig. 1. Patient 17 in group A (sudden death during sport). A, Right coronary angiogram showing proximal occlusion. B, Occlusion is relieved after intracoronary administration of 200 µg nitroglycerin. Eccentric irregular lesion with intracoronary filling defects consistent with thrombi *(arrows)*. C, Forty minutes after intracoronary infusion of streptokinase most thrombi have disappeared.

of more than 90% in 12 patients; between 80% and 90% in 12; between 70% and 80% in three; between 50% and 65% in five, between 30% and 45% in four, and no obstruction at all in a single patient (after intravenous streptokinase). In 11 patients treated with streptokinase before coronary angiography, the residual stenosis of the culprit vessel was between 90% and 99% in five instances; between 60% and 85% in three, and between 0% and 40% in three. Overall a minor to moderate stenosis (0% to 65%) was found in 23.8% of patients.

Coronary thrombosis and lesion morphology. Intracoronary filling defects consistent with thrombi were detected in 12 vessels (28%), either in subtotally obstructed coronary arteries or after reperfusion with streptokinase or nitroglycerin (Figs. 1 and 2). Coronary morphology was determined in 35 vessels with less than 100% and more than 20% obstruction directly or after treatment with nitroglycerin, streptokinase, or both. Concentric lesions were present in six patients, type I eccentric lesions in 11, and type II eccentric lesions in 18. In each group a type II eccentric lesion was the prevailing coronary morphologic feature (Figs. 1 and 2).

Additional findings. Results of coronary angiography also showed associated coronary artery disease in 10 patients (23.8%): two-vessel disease in nine patients and three-vessel disease in one. The atherosclerotic obstruction of the nonculprit coronary artery was 70% to 75% in three patients and between 30% and 50% in five. In the remaining two patients, who had ECG evidence of a previous small myocardial infarction, the vessels were occluded with complete collateral filling. There were no differences in the angiographic findings between the two groups. All patients, with the exception of those with unstable angina and two survivors of sudden death (No. 22 in group A; No. 19 in group B), had a myocardial infarction as determined by ECG and/or enzyme changes. There were no complications related to acutely performed coronary angiography, thrombolytic therapy, and mechanical reperfusion measures in all patients.

DISCUSSION

The present study is the first comprehensive report on acute ischemic syndromes related to sport. It shows that the clinical characteristics and the coro-
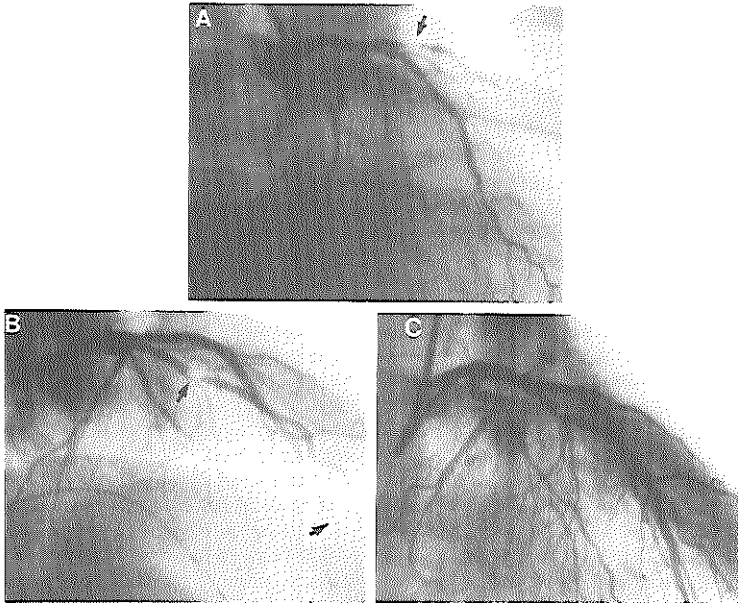
Fig. 2. A, Patient 4 in group B (acute myocardial infarction after sport). Left coronary angiogram showing proximally in left anterior descending artery subtotal eccentric obstruction *(arrow)* with intraluminal filling defect suggestive of thrombus and poor antegrade flow. B, Patient 15 in group B (sudden death after sport). Left coronary angiogram after reperfusion, 30 minutes after intracoronary administration of streptokinase, showing proximal subtotal obstruction in left anterior descending artery *(black arrow)*. Morphology of lesion is eccentric irregular. Left anterior descending artery is distally occluded *(white arrow)*. C, Fifteen minutes after further administration of streptokinase, obstruction has been diminished and distal occlusion has been relieved.

nary angiographic findings of patients with unstable angina, AMI, and sudden death during and after sport are similar; it demonstrates a relationship between the performance of sporting activities and the occurrence of a coronary event; and it suggests a common pathogenesis for the ischemic syndromes related to sport.

The dramatic occurrence of a coronary event in association with sport in previously healthy people raises several questions about the underlying pathogenesis. The mechanism through which sport may induce or precipitate a coronary event is still speculative, and there is no explanation for the time delay before the unexpected onset of symptoms or sudden death after sport. A related social problem is the identification of potential candidates for unstable angina, AMI, or sudden death in the physically active population.

Pathogenesis of acute coronary syndromes. Unstable angina, AMI, and sudden death are clinically defined as acute coronary syndromes, and there is

pathologic evidence that they are just different manifestations of a common acute coronary process.[29-31] Results of necropsy and angiographic studies have shown that the most frequent finding in patients with sudden death and AMI is a (sub)occlusive thrombus.[31-36] The most likely mechanism responsible for the initiation and progression of coronary thrombosis is plaque fissuring or rupture. Plaque rupture with varying degrees of intimal hemorrhage and luminal thrombosis was found on postmortem examination in 95% of patients with unstable angina and AMI who died suddenly.[31, 32] Therefore plaque rupture, by causing intimal hemorrhage, dynamic thrombosis, thromboembolism, and (eventually) spasm, was postulated as the common anatomic pathologic substrate of the three acute ischemic syndromes.

Previous studies. Almost all previous reports on acute ischemic events related to sport are based on postmortem findings and generally concern patients who died suddenly, either during or within 1 hour (or longer) after sport.[1-17] In only a few patients the di-

agnosis of AMI was made after admission to the hospital or before sudden death occurred.[1, 10, 11, 17] Sport has been incriminated as a cause of sudden death mainly in middle-aged people with severe (silent) coronary artery disease. Stenotic coronary arteries with or without acute intimal changes, thrombosis, or both was the most usual finding on pathologic examination in this setting. Remarkably severe obstruction but not total occlusion of the coronary arteries was found in most patients. Both of these latter findings led to the speculation that although coronary spasm could be the cause of sudden death during sport, cardiac arrhythmias resulting from reperfusion of previously ischemic areas may be responsible for sudden death after sport. Coronary thrombosis was indicated as being responsible for silent AMI directly after an exercise test in a 61-year-old woman with diabetes.[37]

Present study. The present report has demonstrated that coronary thrombosis spasm, or both were responsible for coronary occlusion in most of the patients with sudden death and AMI. Indirect evidence of thrombosis was given by coronary patency in 11 patients treated with intravenous streptokinase before coronary angiography. Intracoronary thrombi were visualized in 28% of patients with AMI and sudden death. Furthermore, our data show that in unstable angina, AMI, or sudden death a specific predominant morphology of the culprit coronary artery was found in the form of eccentric lesions types I and II, which are consistent with plaque rupture with or without intraluminal thrombus.[26, 34, 35] In more than 75% of our patients there was isolated single-vessel disease.

Coronary risk factors. Findings in numerous studies have shown that a high percentage of subjects over the age of 30 years in whom exercise-related sudden death occurs have (severe) atherosclerotic coronary artery disease, very often in association with one or more coronary risk factors.[1-17] In addition, endurance exercise does not seem to reduce the coronary risk of middle-aged people with a positive paternal history of coronary artery disease.[38, 39] In our patients the prevalence of cigarette smoking was comparable to that reported in other studies. However, other risk factors, such as family history of coronary artery disease, hypertension, and elevated serum cholesterol levels were often not present. Furthermore, although the majority of patients had at least one coronary risk factor, 23.8% did not. This finding indicates that even healthy sportsmen should not be considered immune to coronary disease and sport-related coronary events.[1-4, 6, 53]

Fixed stenosis, prodromata, and plaque rupture. Inasmuch as thrombotic coronary (sub)occlusion is generally found in the presence of atherosclerotic plaques, the question is whether an important stenosis was preexistent to the coronary event associated with sport. This observation is obviously related to the previous occurrence of symptoms. In fact, with the exception of silent ischemia, an important coronary stenosis is expected to cause anginal complaints during strenuous physical exercise. In contrast to our experience, previous studies have reported a high percentage of prodromata in victims of sudden death.[1-17, 27, 28] This discrepancy can be explained by the fact that our resuscitated victims of sudden death testified themselves. It is conceivable that in other studies the testimony of the relatives could have been influenced by the knowledge of the cause of death. Conversely it has been noted by other investigators that many sportsmen have a tendency to deny or ignore symptoms.[10]

With regard to symptoms related to exercise, a direct or delayed onset of unstable angina, AMI, and sudden death, respectively, implies a corresponding sudden change in coronary flow or the culmination of several coronary changes leading to impairment of flow. Results of recent pathologic studies have shown that subocclusive intraluminal or intraintimal thrombosis can occur at the site of fissuring or rupture of atherosclerotic plaques involving a mean of 50% or less of the vessel diameter.[32, 40] Consequently rupture can develop in plaques that may not be regarded as clinically relevant. Considering the limitations of angiography in evaluating the "fixed stenosis" of acute coronary lesions (e.g., plaques can be enlarged by intraintimal hemorrhage[41]), the present findings showed a minor to moderate (up to 65%) residual stenosis after reperfusion in more than 30% of previously occluded coronary arteries.

Therefore we can reasonably suppose that a significant number of our patients did not have previous symptoms, most probably because they did not have a severe coronary stenosis. Symptoms must have developed as soon as a sudden change in behavior and flow occurred in the culprit coronary artery. We propose that this change was most likely represented by exercise-precipitated plaque rupture. Rupture of a minor or moderate atherosclerotic plaque can subsequently lead to coronary subocclusion through thrombosis, spasm, or both. Recently we were able to substantiate this hypothesis by the demonstration of subtotal occlusion of a previously normal or moderately stenotic coronary artery shortly after a normal exercise stress test in four patients.[42] In two previous reports we also propose that plaque rupture could be the etiologic factor of AMI and sudden death after sport.[43, 44]

Platelets. Platelets have been implicated in the

participation of acute coronary syndromes.[45-47] The role of exercise-related platelet activation in the manifestation of acute coronary disease is still controversial and speculative. There have been conflicting reports on exercise-related inhibition or activation of platelet aggregation.[48-52] However, evidence has been produced that activation and aggregation of platelets occurs if the endothelium fails to function properly, as when it is damaged by disruption of an atheromatous plaque.[31-33, 47]

Vasospasm. Coronary reperfusion after intracoronary administration of nitroglycerin in five of our patients demonstrated the presence of coronary spasm at the site of occlusion. In three of five patients with coronary spasm there was also evidence of coronary thrombi. Furthermore, in five patients with reperfusion after intracoronary streptokinase and in one patient with coronary spasm the residual obstruction ranged from 30% to 65%, indicating that either coronary spasm or thrombosis or both played a major role in the development of coronary occlusion.

These findings, however, do not indicate that coronary spasm was the etiologic factor.[24, 53, 54] The presence of vasospasm in the setting of acute coronary artery diseases[24] seems to be the result of the changes evoked by a damaged intima.[30, 47] However, the occurrence of primary coronary vasospasm has been documented during or shortly after exercise in patients with or without evidence of coronary atherosclerosis.[24, 55, 56] In one study coronary vasoconstriction was demonstrated during dynamic exercise because of active vasospasm.[56] The mechanism of exercise-induced narrowing of diseased coronary arteries could be related to unopposed α-adrenergic stimulation by circulating catecholamines as a result of segmental endothelial dysfunction.[56, 57]

Vasomotion and plaque rupture. Inasmuch as physical exercise can induce vasospasm of a diseased coronary segment, one can hypothesize that coronary vasomotion may represent the trigger responsible for plaque rupture. If during exercise vasoconstriction occurs at the site of an atherosclerotic plaque, where normal wall properties are diminished or abolished, the repeated kinking of the vessel could cause intimal plaque fissuring or rupture. This event can take place at the site of a minor or moderate coronary stenosis.[32, 40]

As a result of plaque rupture a series of dynamic changes can be initiated involving intraintimal hemorrhage and/or luminal thrombosis and/or intracoronary embolization and/or spasm, or all of them, with the potential of producing the clinical manifestation of unstable angina, AMI, and sudden death.[32] If the dynamic changes evolve, leading to subtotal coronary occlusion, this process can develop rapidly or over a relatively short period of time.[41] This characteristic can explain both the sudden onset of pain or death during exercise and the time delay before the onset of symptoms after sport. Therefore the culmination of temporary clinically silent coronary changes initiated by exercise-induced plaque rupture can be responsible for the delayed manifestation of coronary events after exercise.

Implications. The use of ECG stress testing for the detection of subjects at risk among physically active asymptomatic people has important limitations.[57-59] In addition, AMI and sudden death may occur despite normal results of exercise tests and little or no angiographic evidence of coronary arteriosclerosis.[42, 63] Our present data and previously reported findings suggest that no severe coronary disease was present in a significant number of our patients before their last sporting activity. Exercise itself, by inducing a series of intracoronary changes, probably produced the necessary conditions for an acute coronary event. Such an event may therefore be considered unexpected and unpredictable. This hypothesis may partially justify the absence of symptoms and the inability of the ECG to show myocardial ischemia during a stress test, and it may also explain the low percentage of prodromata encountered in our patients. Our findings do not diminish the usefulness and the role of periodic ECG exercise stress testing in detecting silent ischemia in well-trained, middle-aged people.[64, 65] However, the incidence of false positive test findings in sportsmen can be high (25%).[66] Nevertheless, the value of exercise ECGs can be increased when their sensitivity is also increased.[63, 67-69] Furthermore, it is very important to inform people engaged in sporting activities about the possible occurrence of cardiac symptoms.[70] From the epidemiologic point of view there is no reason to discourage sport or heavy physical work or leisure-time activity, which can help in preventing premature death even in the presence of all known coronary risk factors.[71, 72] Our finding of coronary occlusion in almost all survivors of sudden death cannot support the hypothesis that reperfusion arrhythmias are the cause of these deaths.

Limitations of the study. The most significant limitation is the lack of a control group of nonconditioned people with unstable angina, AMI, and sudden death for comparison. Second, the data presented may not be representative for all patients with exercise-related coronary events, considering the fact that we only studied subjects with myocardial ischemia. We do not have comparative acute data on resuscitated victims of cardiac arrest resulting from transient myocardial ischemia or other coronary or myocardial

causes.[73-76] Third, our results do not necessarily demonstrate a direct cause-effect relationship between sport and coronary events. We did, however, encounter a subject with recurrent AMI and sudden death after sport[44] in whom the relationship could hardly be considered merely coincidental. Fourth, the absence of prodromal symptoms in most of our patients does not exclude the possibility that silent ischemia occurred before their coronary event.

Finally the suggestion of plaque rupture as the likely cause of exercise-related coronary syndromes are based on a descriptive analysis of coronary lesions. However, a good correlation has been demonstrated between postmortem angiography and the pathologic finding of plaque rupture and thrombus.[35] Findings in recent clinical angiographic studies have suggested the same correlation in patients with unstable angina and AMI.[26, 34] Predominance of either intraluminal thrombosis or initial hemorrhage was probably responsible for the inability to visualize eccentric lesions in all patients.[26, 32, 40] Predominance of intimal hemorrhage may also explain the failure of reperfusion attempts in two patients.[32, 77]

Conclusions. This study constitutes the first acute coronary angiographic demonstration of a continuous spectrum of acute ischemic events related to sport. The predominant coronary feature of acute syndromes related to sport is an eccentric lesion that is often associated with thrombosis and less frequently with thrombosis and vasospasm. Physical exercise, probably through coronary spasm, may induce plaque rupture, which in turn can lead to coronary (sub)occlusion precipitating an acute coronary event. Such an event is in most instances unexpected and unpredictable. However, early recognition of risk factors for coronary artery disease and periodic evaluation can identify high-risk subjects. The mechanism proposed its hypothetical and needs to be validated by further studies.

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RECURRENT ACUTE MYOCARDIAL INFARCTION DURING SPORT

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ABSTRACT

A 48 year old well conditioned man developed acute myocardial infarction (AMI) twice during sporting activities.

Right coronary angiography after the first AMI showed a proximal moderate stenosis and five months later, after the second AMI, a subtotal obstruction distally at the site of prior slight lumen irregularity. This case suggests a causal relationship between sport and the occurrence of acute coronary events.

INTRODUCTION

Numerous reports have focused on the occurrence of cardiac arrest and non-fatal acute coronary events related to sport (1-3). Severe obstructive coronary artery disease is the predominant pathological finding in middle-aged victims of sport related sudden death (1,2). However non evident or minor obstructive disease was shown in some survivors of exercise-related acute coronary syndromes (3,4). The mechanism of these events still remains inconclusive. We report the case of a conditioned man who developed acute myocardial infarction (AMI) twice during sport. The findings in this case can help us to understand the occurrence of acute coronary events related to vigorous exercise.

CASE REPORT

A 48-year old previously healthy man was admitted because of chest pain which started while playing volleyball. Although he used to play more often during his youth he was now engaged in competitions for at least 2 hours a week and raced on his bicycle 20 km a day. He smoked 5 cigarettes a day for 3 years but had no other coronary risk factors nor prodromal symptoms suggestive of angina pectoris. On admission physical examination and

routine investigations were normal. The electrocardiogram (ECG) showed ST segment elevation in leads II,III, aVF,I,aVL,V5,V6. In view of acute myocardial infarction (AMI) the patient received $1.5X10^6$ U streptokinase intravenously over 45 min, about 90 min. after the onset of symptoms. After 30 min. there was relief of pain and normalization of the ECG. He developed a non-Q wave myocardial infarction with a peak serum creatine phosphokinase (CPK) of 359 U/l (normal < 210 U/l) and had an uncomplicated course. After discharge an exercise stress test was normal and the patient remained asymptomatic. Coronary angiography was performed 4 months later for assessment of coronary risk before allowing him to resume sporting activities. The left coronary artery showed no evidence of obstructive disease. The right coronary artery (Fig.1a) showed proximally a moderate irregular lesion and slight lumen irregularities in the periphery. The patient resumed his sporting activities. He remained asymptomatic until 5 months later when he developed again chest pain during a bicycle race. He was readmitted because of recurrent infero-lateral AMI. About 1 hour after the onset of symptons he received $1.5X10^6$ U urokinase intravenously over 15 min. Seventy min. later pain was relieved and the ECG normalized. The patient developed a non-Q wave myocardial infarction with a peak serum CPK of 860 U/l. Coronary angiography, six days later, showed an unchanged left coronary artery and in the right coronary artery a subtotal concentric lesion proximal to the crux (Fig 1b). Balloon angioplasty of this lesion was successfully performed. During 11 months follow-up the patient is still doing well. Repeat exercise stress tests were normal but he has not resumed his sporting activities.
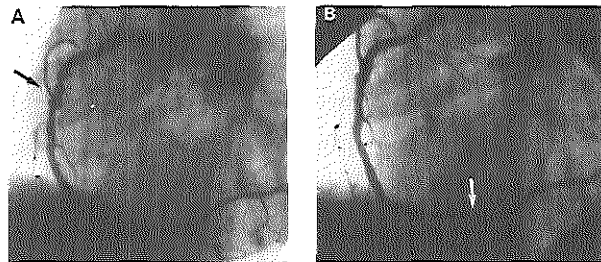

Fig 1 Right coronary angiograms after thrombolytic therapy for recurrent acute myocardial infarction (AMI) during sport. After the first AMI: proximally a moderate irregular lesion and distally slight lumen irregularities A. Five months later, after the second AMI: distally there is a subtotal stenosis B.

DISCUSSION

This report emphasizes the paradox of healthy physical performance and the abrupt occurrence of an acute coronary event. The recurrence of AMI during sport in the same subject has not been previously reported. The present case is complementary to our previous report of recurrent AMI and sudden death after sport (4). Some clinicopathologic and epidemiologic studies have shown that sudden death occurred during or immediately after strenous exertion more often than expected by chance (5). Although in previous pathologic studies sport-related sudden ischemic death was associated with severe coronary artery disease (1,2) in the present case, as in some others (3-4), a moderate stenosis was shown in the culprit coronary artery after thrombolytic therapy. This finding indicates that severe coronary artery disease is not a prerequisite for sport-related ischemic events.

Conversely, in our patient, after the second AMI a severe obstruction was present at the site of a previous slight stenosis. Intraintimal haemorrhage associated with plaque rupture can explain the angiographic finding of subtotal vessel obstruction inspite of thrombolytic therapy (4,6). An alternative explanation could be that the minor stenosis had increased leading, coincidentally during sport, to the occurence of the second AMI. However, the absence of anginal symptoms prior to both events and the coronary angiographic findings after the first AMI support the clinical suggestion of exercise-precipitated acute coronary occlusion for both events.

Although some conditioned previously healthy subjects can unexpectedly develop an acute coronary syndrome associated with sport, the mechanism of these events is still hypothetical (4). Moreover, it is unknown how many of these subjects are potential candidates for a recurrent event after resuming sporting activities. Therefore, it can be premature and unjustified to advise patients who experienced acute myocardial infarction during or shortly after sport to refrain from their sporting activities.

In this category of patients regular medical control with periodic exercise stress-testing could identify subjects at risk and prevent the recurrence of coronary events.

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CHAPTER 6

CLINICAL AND ANGIOGRAPHIC OBSERVATIONS ON
RESUSCITATED VICTIMS OF EXERCISE-RELATED
SUDDEN ISCHEMIC DEATH

Clinical and Angiographic Observations on Resuscitated Victims of Exercise-Related Sudden Ischemic Death

Renzo Ciampricotti, MD, Rob Taverne, MD, and Mamdouh El Gamal, MD

The clinical and angiographic findings of 17 re-suscitated victims of exercise-related sudden ischemic death are reported in an attempt to elucidate the mechanism(s) of these deaths. Ten survivors developed cardiac arrest during or after sporting activities (group A) and 7 others during or after an exercise stress test (group B). There were 15 men and 2 women. The mean age of group A was 46 years and of group B 55 years. Coronary risk factors, as well as previous angina and myocardial infarction, were more frequent in group B. Only 3 of the 17 survivors had anginal symptoms before sudden death. Sudden death in group A was associated with acute myocardial infarction in 8 and unstable angina in 2 and was associated in group B with acute myocardial infarction in 2, unstable angina in 3 and silent ischemia in 2. Coronary angiography was acutely performed in 15 patients. In most patients the ischemia-related coronary artery was totally or subtotally occluded. Clinical and angiographic findings indicate that exercise-related sudden ischemic death was due to an acute coronary event—in most cases unexpected and unpredictable. It is suggested that exercise-induced intracoronary changes were probably responsible for the development of acute coronary (sub)occlusion and sudden death.

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Numerous pathologic studies have shown that sudden death in subjects >40 years old is mainly associated with coronary artery disease.[1-3] Therefore, myocardial ischemia is believed to be essential in precipitating most episodes of sudden death. Physical exercise has been indicated as a contributing factor in the occurrence of a relevant number of sudden deaths.[4-6] The current opinion is that subjects prone to developing exercise-related sudden death have either known or unknown preexistent important coronary artery disease.[7-15] The precise pathophysiologic aspects of these cardiac arrests still remain uncertain.[16-18] Furthermore, exercise-related sudden death very often occurs unexpectedly and without prior warning symptoms in previously healthy subjects. This study attempts to elucidate the mechanism(s) of exercise-related sudden ischemic death.

METHODS

Patients: The study population comprised 17 patients, resuscitated victims of cardiac arrest. Ten patients (group A) survived out-of-hospital sudden death related to sporting activities and 7 patients (group B) were resuscitated from sudden death occurring during or after an exercise stress test. All but 1 of group A patients had neither a medical history nor symptoms suggestive of angina pectoris. All group A patients were well-conditioned, habitually sportive subjects. In group B, 5 of 7 patients had a history of angina or myocardial infarction. The patients underwent exercise stress testing for screening of cardiac disease (n = 2), evaluation of anginal complaints (n = 2), or routine control of ischemia >1 month after myocardial infarction (n = 3). Coronary risk factors in group A patients were cigarette smoking in 5 and hypertension (diastolic blood pressure >90 mm Hg) in 1; in group B patients, they were cigarette smoking in 5 and hypercholesterolemia (>240 mg/dl) in 2. Sudden death occurred in group A patients during sport in 6 and after sport in 4. In group B patients, sudden death occurred during the exercise test in 1 and thereafter in 6.

Definitions: Myocardial ischemia detected on the electrocardiogram was defined as ≥1 mm ST-segment elevation or depression in ≥3 contiguous leads.[19] Unstable angina was diagnosed when myocardial isch-

emia, lasting >15 minutes, was relieved at least temporarily after intravenous administration of nitroglycerin and was not associated with an increase in serum creatine kinase MB fractions. The diagnosis of acute myocardial infarction was made when myocardial ischemia lasted >30 minutes and persisted after intravenous administration of nitroglycerin, together with an increase in serum creatine kinase MB fractions and either with or without development of new Q waves on the electrocardiogram. Silent or asymptomatic myocardial ischemia was diagnosed as electrocardiographically detected ischemia lasting for ≥1 minute in conscious patients without an increase in serum creatine kinase MB fractions. Sudden ischemic death was defined as being unexpected witnessed death heralded by cardiocirculatory and respiratory arrest that occurred during or within 1 hour after physical exertion, related to electrocardiographically detected myocardial ischemia. Resuscitated victims (survivors) of sudden death were patients in whom cardiopulmonary resuscitation with or without medical or electrical intervention, or both, reestablished cardiac activity and circulation.

Procedures: The exercise stress test was performed on an upright bicycle ergometer, using a modified Bruce protocol.[20] A 12-lead electrocardiogram was continuously monitored during the test and up to 4 minutes after it. Blood pressure was measured every 2 minutes during and after the test and at maximal exercise tolerance. After informed consent was received from patients or their relatives, coronary angiography was performed in patients with acute myocardial infarction within 90 minutes and in patients with unstable angina within 3 hours after resuscitation, but was delayed (within 3 days) in patients with silent ischemia. Selective coronary and left ventricular angiography was performed using standard techniques. The left and right coronary arteries were visualized in ≥2 different views. Quantitative determination of coronary stenosis was made by comparing the stenotic segment with an adjacent normal segment proximal and distal to the lesion. The degree of collateral filling of an occluded coronary artery by ipsilateral or contralateral collateral vessels was determined according to the classification of Cohen et al[21] (from grade 0 [no collateral vessels] to grade III [complete filling of the vessel]). All electrocardiograms and coronary angiograms were blindly reviewed by 3 experienced cardiologists. The ischemia-related coronary artery was identified when the ischemic localization on the electrocardiogram corresponded with the anatomic region that was shown to be supplied by a (severely) diseased coronary artery.

RESULTS

Patient data: The arrhythmia monitored at resuscitation for group A was ventricular fibrillation in 8,

asystole in 1 and undetermined in 1; for group B, it was ventricular fibrillation in 3, ventricular tachycardia or flutter in 3 and asystole in 1. In group A patients, sudden death occurred during or after sport without symptoms in 8 and preceded by anginal complaints a few minutes before collapse in 2. Symptoms or cardiac arrest, or both, occurred in 4 patients, 20 to 45 minutes after the end of sporting activities. After resuscitation, 8 patients were shown to have acute myocardial infarction, whereas 2 presented with unstable angina. In group B sudden death occurred with directly preceding anginal complaints in 2 patients with out-of-hospital cardiac arrest who were shown to have acute myocardial infarction after resuscitation, 60 and 45 minutes, respectively, after a normal exercise test. Three patients collapsed shortly (3 and 4 minutes) after a normal exercise test, but developed unstable angina after resuscitation. Two patients had silent ischemia before cardiac arrest occurred, but there was no evidence of ischemia on the electrocardiogram after resuscitation. The ischemic localization on the electrocardiogram corresponded in all cases with obstruction or occlusion of the expected ischemia-related coronary artery.

Angiographic data: The coronary angiographic findings of group A and B patients in relation to diagnosis and electrocardiographic changes during and after exercise testing are listed in Table I. GROUP A: At coronary angiography, all coronary arteries were occluded, except in 2 patients whose arteries were patent after intravenous administration of streptokinase before angiography. In these 2, reperfusion most probably occurred before catheterization, as suggested by the normalization of the ST segments on the electrocardiogram after streptokinase therapy. In the 2 patients with unstable angina, the coronary artery was occluded but filled by collateral supply. Associated coronary artery disease was present in 2 patients, 1 of whom had previously had a small myocardial infarction. Reperfusion and revascularization were successfully performed in all but 2 patients (nos. 5 and 6). One (no. 5), who had an occluded, collaterally filled coronary artery, was treated with a β blocker. One to 2 months after resuscitation, a symptom-limited exercise stress test was normal in all patients. GROUP B: No abnormal responses were observed during the exercise test in all but 2 patients who had ischemia on the electrocardiogram without anginal complaints. At coronary angiography, 2 patients with acute myocardial infarction (nos. 1 and 2) had occlusion of the infarct-related coronary artery. In the patient with partial collateral filling of the occluded artery, attempts to reperfuse the vessel were unsuccessful. This patient had a positive exercise test 3 months later. Of 3 patients who developed unstable angina (nos. 3 to 5), 2 had severe stenosis and 1 an occlusion of the ischemia-related coronary artery. In the latter, the artery

TABLE I Electrocardiographic and Coronary Angiographic Data of Survivors of Sudden Ischemic Death Related to Sport (group A) and to Exercise Testing (group B)

Pt. No.	ET ECG	PCPR ECG	Diagnosis	IRCA	% of Stenosis	ACD	Previous AMI
			Group A				
1	—	ST↑A	UA	LAD	100'	Right 100%	I
2	—	ST↑A	UA	LAD	100'	0	0
3	—	ST↑A	AMI	LAD	100	0	0
4	—	ST↑A	AMI	LAD	100	0	0
5	—	ST↓A	AMI	LC	100†	0	0
6	—	ST↑A	AMI	LAD	40*	0	0
7	—	ST↑A	AMI	Right	95*	0	0
8	—	ST↑A	AMI	LAD	100	0	0
9	—	ST↓A	AMI	LC	100	LAD 50%	0
10	—	ST↑A	AMI	Right	100	0	0
			Group B				
1	N	ST↑A	AMI	LAD	100	Right 30%	0
2	N	ST↑A	AMI	LAD	100†	Right 40%	0
3	N	ST↓A–I	UA	IM	90	0	0
4	N	ST↓A–I	UA	IM	99	LAD 80%, right 50%	A
5	N	ST↑I	UA	Right	100'	0	I
6	ST↓L	N	SI	OM	99†	Right 50%	I
7	ST↑I	N	SI	Right	100†	0	0

*After streptokinase therapy.
'Completely and †partially filled by collateral flow.
A = anterior; ACD = associated coronary disease; AMI = acute myocardial infarction; ECG = electrocardiogram; ET = exercise testing; I = inferior; IM = intermediate artery; IRCA = ischemia-related coronary artery; L = lateral; LAD = left anterior descending artery; LC = left circumflex artery; N = normal; OM = obtuse marginal artery; PCPR = postcardiopulmonary resuscitation; SI = silent ischemia; ST ↑ and ↓ = ST-segment elevation and depression; UA = unstable angina.

was filled by collateral supply. Of the 2 patients with asymptomatic ischemia (nos. 6 and 7), 1 collapsed at almost maximal predicted exercise tolerance, while the other collapsed during the recovery period after further increase of asymptomatic ischemia. In both cases, there were no signs of ischemia on the electrocardiogram after resuscitation. One patient had subtotal occlusion and the other total occlusion of the coronary artery involved. There was complete collateral filling of both vessels. Three patients (nos. 1, 3 and 4) underwent reperfusion of the ischemia-related coronary artery, while the other patients were treated with a β blocker. One to 3 months after resuscitation, all but 1 patient (no. 2) had a repeat normal exercise test. The distribution of (sub)occluded arteries was similar in both groups of patients, with sudden death occurring either during or after exertion. In both groups, left ventricular angiographic study revealed localized hypokinesia or akinesia corresponding to the infarct- or ischemia-related coronary artery. There were no ventricular abnormalities related to the culprit coronary artery in 4 patients with unstable angina and in the 2 patients with silent ischemia. There were no complications associated with the performance of coronary and left ventricular angiographic studies in any patients.

DISCUSSION

A considerable percentage (varying from 10 to 60%) of all sudden deaths has been reported as occurring during or after moderate and high-level physical activity.[6-9] In people aged >30 years, exercise-related sudden death is generally associated with 1- or multiple-vessel coronary artery disease and frequently also with myocardial scars.[1-6] Pathological examination of the coronary arteries revealed either fresh subocclusive thrombi or acute intimal lesions in 15 to 80% of cases.[1-15] However, acute coronary angiographic studies in this setting are lacking[22] and the pathophysiology of exercise-related sudden death remains speculative.[18] The present study shows that exercise-related sudden death can be caused by an acute coronary event that clinically can present as unstable angina, acute myocardial infarction and transient silent ischemia. The 2 groups of patients studied had in common the unexpected development of sudden death related to physical exertion. Furthermore, clinical and electrocardiographic data of patients having an exercise test provided information helpful in understanding the mechanism of these deaths.

With regard to sudden death associated with unstable angina and acute myocardial infarction, the patients undergoing the exercise test did not have ischemia and had no complaints. After the test there was a time delay before the development of ischemia, symptoms and sudden death. In the victims of sudden death related to sport, when symptoms occurred, either during or after sport, they ensued just before the development of cardiac arrest. The question relevant to the pathophysiology is how to explain the unexpected onset of symptoms or sudden death, or both. The finding of ischemia after resuscitation following a normal exercise test indicates that the onset of symptoms or sudden death, or both,

were due to sudden (sub)total impairment of coronary flow. Acute coronary angiography in patients with unstable angina and acute myocardial infarction confirmed this expectation. Exercise can provoke active vasomotion of diseased coronary arteries with activation of platelet aggregation and impairment of coronary flow.[23,24] It can also be hypothesized that active repeated coronary spasm during exercise can provoke fissuring or rupture of atherosclerotic plaques, leading to coronary (sub)occlusion by intraintimal hemorrhage or intracoronary thrombus formation, or both.[22,25,26] Recently, exercise-induced plaque rupture was suggested as the mechanism of coronary (sub)occlusion after a normal exercise test in 4 patients with previously normal or moderately narrowed coronary arteries.[27] Although silent ischemia is a usual finding in survivors of sudden death, life-threatening ventricular arrhythmias rarely occur during exercise testing.[28-30] Cardiac arrest was related to exercise-induced silent ischemia in 2 of our patients. The disappearance of ischemia after resuscitation implied restoration of myocardial perfusion. Their angiographic findings suggest that acute silent ischemia and cardiac arrest occurred as a result of acute coronary (sub)occlusion. The collateral filling of the vessels avoided myocardial damage, restored myocardial function and relieved ischemia on the electrocardiogram. The clinical and angiographic findings of the resuscitated victims of this study suggest that exercise itself unexpectedly induced intracoronary changes responsible for coronary (sub)occlusion. The observations of this study are limited by the lack of a control group of survivors of sudden death unrelated to exercise. Furthermore, no electrophysiologic study was performed to exclude enhanced electrical instability.

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CHAPTER 7

CHARACTERISTICS OF CONDITIONED AND

SEDENTARY PEOPLE WITH ACUTE CORONARY SYNDROMES

CHARACTERISTICS OF CONDITIONED AND SEDENTARY PEOPLE
WITH ACUTE CORONARY SYNDROMES

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ABSTRACT

The role of habitual exertion in the development and manifestation of atherosclerotic coronary artery disease is still undetermined. We compared, in a case-control study, 36 well-conditioned men developing acute coronary syndromes related to sport with 36 sedentary men with the same coronary syndromes occurring at rest. The mean age of the study subjects was 48 years (range 25-65). There were 8 patients with unstable angina, 46 with acute myocardial infarction and 18 survivors of sudden ischemic death. The cases exercised on average 6 hours per week for at least 10 years. Coronary angiography was performed in all patients within 4 hours after the onset of symptoms. Sporting subjects had less risk factors than their sedentary counterparts: fewer of them smoked (56% vs 95%) or had cholesterol levels $\geq$ 240 mg/dl (12% vs 56%, both $p < 0.05$). Prodromal symptoms were more prevalent among sedentary subjects (48% vs 9%, $p < 0.04$). In addition, sedentary patients more often had multiple vessel coronary artery disease. (73% vs 28%, $p < 0.02$) None of the sporting subjects died in-hospital compared to 3 sedentary subjects: 10 sedentary and 5 active patients underwent by-pass surgery during hospital stay. There were no differences between the two groups with regard to site, morphology and presence of thrombus of the culprit artery and diameter and dominance of all coronary arteries. After 2 year follow-up new coronary events had occurred more frequently in sedentary subjects (10 vs 6). This study demonstrates a common pathogenesis for acute coronary syndromes related and unrelated to sport. However, the precipitating factor(s) for syndromes related to sport may be different. Regular vigorous exertion is associated with less

coronary risk factors and extent and severity of coronary artery disease, but can unexpectedly provoke an acute coronary syndrome in some conditioned people.

INTRODUCTION

Coronary artery disease is the main cause of death related to exercise in middle-aged people (1-11). Whilst a protective effect against coronary disease and death has been attributed to regular physical activity (12-18), conversely acute myocardial infarction and sudden death have been associated in strict relation to vigorous exertion (19-32). However, these observational studies did not provide definitive evidence of a favourable influence of physical exercise on coronary artery disease nor were they able to establish a causal relationship between exertion and acute coronary events.

On the other hand physical inactivity can be reasonably regarded as an independent and modifiable coronary risk factor. (32a)

Recently a continuous spectrum of acute ischemic events was demonstrated in association with physical exercise and exercise-induced plaque rupture was hypothesized as the mechanism of these events (33-34). However, plaque rupture is a common angiographic and pathological feature in patients with acute coronary syndromes (35-37). The present study compares the clinical and acute coronary angiographic characteristics of 36 conditioned men to those of 36 sedentary men, with acute coronary syndromes occurring respectively in relation to sport, and at rest. This analysis may detect peculiarities proper to physically active people and clarify the mechanism of acute coronary events associated with vigorous exertion.

METHODS

Patients. The study was designed as a case-control study with 36 cases and 36 control subjects (Table 1). The cases were well trained, conditioned previously healthy men who were admitted for acute coronary syndromes occurring during or within the first hour following sport activities in a five year period from 1985 to 1990. Coronary angiography was performed within 4 hours after the onset of symptoms. The cases exercised on average 6 hours per week for at least 10 years. The controls were selected from

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admissions at the same hospitals during the identical time period. They were matched with regard to sex, age, previous health, coronary syndrome, date of admission (within one year), coronary angiography within 4 hours after the onset of symptoms, but differed from the cases in that they were all not physically active and their coronary syndromes occurred at rest.

TABLE 1 BASELINE CHARACTERISTICS

Group	Sporting	Sedentary
N°	36	36
Sex	M	M
Age (years)		
25 - 40	11	13
41 - 55	22	20
56 - 65	3	3
Diagnosis		
UA	4	4
AMI	23	23
SD	9	9

AMI = acute myocardial infarction; M = male; UA = unstable angina; SD = sudden death.

Admission diagnosis.   Unstable angina was diagnosed when chest pain, associated with ST-T segment changes on the electrocardiogram was relieved at least temporarily by sublingual or intravenous administration of nitro-glycerin.   The diagnosis of acute myocardial infarction was based on the persistence of chest pain and $\geq$ 2 mm ST-segment elevation and/or depression in two or more contiguous leads on the electrocardiogram despite the administration of intravenous nitroglycerin (39).   Survivors of sudden ischemic death were those patients, resuscitated from unexpected natural witnessed death, occurring either with or without preceding symptoms, with electrocardiographic evidence of ischemic changes compatible with acute myocardial infarction.   The laboratory diagnosis of myocardial infarction was made in the presence of a typical pattern of cardiac enzymes elevation. The maximal serum creatine level was registered.

Treatment protocol. Immediately following admission all patients received intravenous nitroglycerin (> 15 μg/kg/m), heparine (5.000 U), aspirin (250

mg) and dexamethasone (12 mg). The electrocardiogram was repeated after five minutes. If transmural myocardial ischemia persisted, at the discretion of the investigator, coronary angiography was in some cases preceded by the intravenous infusion of 1.5×10^6 U of streptokinase over 30 minutes. At angiography, if the ischemia-related coronary artery was found to be occluded, 0.2 mg of nitroglycerin was administered intracoronarily and coronary angiography was repeated. Intracoronary infusion of streptokinase was then started at a rate of 5000 U/min. until a total dose of 250,000 U was given. Mechanical reperfusion and balloon angioplasty were immediately attempted in case of coronary occlusion or after failure of intracoronary streptokinase therapy.

Clinical and angiographic data. Laboratory determinations of haemoglobin, renal and liver function, electrolytes, platelet count, fibrinogen and prothrombin time and total cholesterol levels were performed twice in all patients. Hypercholesterolemia was defined as a total serum cholesterol level $\geq$ 6 mmol/l ($\geq$ 240 mg/dl). During their hospital stay all patients answered a questionnaire related to their family history of coronary artery disease, smoking habits and symptoms before their cardiac event. Both typical and atypical anginal complaints were classified as angina pectoris (40-41). The time of onset of symptoms or sudden death was also recorded (42,43). All electrocardiograms and coronary angiograms were reviewed by three experienced cardiologists, independently and blinded to the clinical data. Disagreement was resolved by consensus.

The ischemia-related coronary artery was identified by the correspondence between electrocardiographic changes, coronary angiographic findings and left ventricular wall motion abnormalities, or both. The presence of coronary spasm was deduced when intracoronary administration of nitroglycerin resulted in opening of a previously occluded coronary artery (44). Intracoronary filling defects were defined as being consistent with thrombus if they appeared spherical, ovoid, or irregular outlined by contrast medium (45). The morphology of coronary artery lesions was described as either concentric or eccentric with regular or irregular borders. Eccentric lesions were considered to be consistent with ruptured plaques with or without thrombosis (36,37). The lesion morphology was determined

directly in patent vessels or directly after reperfusion achieved with nitroglycerin or streptokinase.

Quantitative determination of diameter stenosis or residual stenosis of patent and non-mechanically reperfused culprit coronary arteries was made by measuring the stenotic segment and comparing it with the mean of normal segments proximal and distal to the lesion on an end-diastolic frame in at least two different angiographic projections. The presence and severity of stenoses in other vessels of the coronary system was also recorded. The site of occlusion or obstruction on the culprit coronary artery was defined in proximal, mid, and distal segments. The luminal diameter of the coronary arteries was measured directly beyond their origin in the same standardized angiographic view, using as reference the true size of the coronary catheter. Vessel dominance was defined as left, or right, or balanced, depending on whether the ramus descendens posterior and most posterolateral branches stemmed respectively from the left circumflex branch or the right coronary artery or both (46). The grading of ipsilateral and contralateral collateral filling of (sub)occluded coronary arteries was determined as 0(no collaterals) up to grade III (complete filling of the vessel) (47).

Data analysis. Continuous variables were compared using Student's t test. P values < 0.05 were considered significant. Odds ratios were calculated to compare categorical variables. The precision of the odds ratios is described with 95% confidence intervals (48).

RESULTS

Clinical characteristics. The clinical characteristics of the 72 patients (36 sporting group, and 36 sedentary group) are summarized in Table 2. Significant differences were observed between the two groups with regard to smoking habits, hypercholesterolemia, prodromal symptoms and time of occurrence of the coronary syndrome. Hypertension was borderline and untreated in 6 out of 7 sportsmen, but required treatment in 10 out of 11 patients of the control group. Eight sportsmen had no identifiable risk factors. An old, apparently silent myocardial infarction was detected in 2 patients of the sport group and in 5 of the sedentary group. The mean time interval between the onset of symptoms or sudden death and coronary angiography was shorter in the sporting group (119 min. vs 151 min.) Chest

pain preceded the development of sudden death in all patients of the control group, but in only three subjects of the sporting group. The mean cardiopulmonary resuscitation time was longer in the control group (20 min. vs 12 min.), as well as the number of defibrillations (3.5 vs 2.3). The distribution of the localization of ischemia on the electrocardiogram was

TABLE 2 CLINICAL CHARACTERISTICS				
Group	Sporting	Sedentary	OR	95% CI
N°	36	36		
ECG ischemia				
Anterior	56%	48%	1.40	0.50,3.9
Diastolic BP				
≥ 90 m Hg	20%	31%	0.55	0.16,1.84
Cholesterol				
≥ 240 mg/l	12%	56%	0.10	0.02,0.38
Family CAD	25%	39%	0.52	0.17,1.60
Cigarettes				
smoking	56%	95%	0.07	0.01,0.39
Prodromata	9%	48%	0.10	0.02,0.44
Time occurrence				
events (hours)				
6 - 12	37%	75%	0.19	0.1 , 0.6

BP = blood pressure; CAD = coronary artery disease; CI = confidence interval; OR = odds ratio.

similar in both groups. In the sporting group 13 events occurred between 9 a.m. and 12 a.m., while 23 events took place between 2 p.m. and 7 p.m. Sudden death occurred in all but one in the afternoon. All patients exercised at a set time of the day. In the control group most events occurred early in the morning and in the evening. Sudden death occurred in all but two in the morning.

Culprit coronary artery and clinical outcome. The reperfusion measures and the patients'clinical outcome are listed in Table 3. The distribution of

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the culprit coronary artery was similar in both groups. All but 7 patients of both groups admitted with evolving myocardial infarction were treated with intravenous or intracoronary streptokinase or both. In three sportsmen reperfusion resulted after intracoronary administration of nitroglycerin, indicating the presence of coronary spasm. Most occluded vessels were reperfused after intracoronary streptokinase administration or mechanically (N=7). Four vessels remained occluded despite reperfusion attempts.

The patients admitted with transmural myocardial ischemia developed a myocardial infarction, excepted two sportsmen resuscitated from sudden death. Peak creatine phosphokinase level in these patients was not different between the two groups.

TABLE 3 CULPRIT CORONARY ARTERY AND CLINICAL OUTCOME		
Group	Sporting	Sedentary
N°	36	36
Streptokinase *	28	30
Ischemia related CA		
LAD	17	19
LCx	5	2
Right	14	15
Patent	18	13
Occluded	18	23
Reperfused	17	20
CPK↑	31	34
PTCA	21	20
CABG	5	10
Death	0	3

AMI = acute myocardial infarction; CA = coronary artery CABG = bypass surgery; CPK↑ = elevated creatine phospokinase; LCx = left circumflex artery; LAD = left anterior descending artery; OM = obtuse marginal artery; PTCA = coronary angioplasty; UA = unstable angina; SD=sudden death; * =intravenous and intracoronary, or both.

Coronary angioplasty was performed in more than 50% of patients of both groups. Ten patients of the control group underwent coronary bypass surgery, compared to five patients of the sporting group. Three survivors of sudden death of the control group died in hospital. Two of these due to recurrent untreatable ventricular fibrillation, 3 hours and 12 days after initially succesful angioplasty. The third patient died ten days after

admission of irreversible cerebral damage due to hypoxia.

Coronary angiographic data. The main findings of the analysis of the coronary angiograms are listed in Table 4. The size of the coronary arteries was similar in both groups with the exception of the right coronary which was larger in the sport group. The number of patients with single-vessel disease was significantly higher in the sporting group, while a significantly higher number of patients of the sedentary group had 2- or 3- vessel disease.

TABLE 4 CORONARY ANGIOGRAPHIC DATA				
Group	Sporting	Sedentary	p value	
Nº	36	36		
Size of CA*(mm)				
LMS	4.30±0.44	4.27±0.44	0.90	
LAD	3.37±0.54	3.22±0.44	0.20	
LCx	2.90±0.44	2.91±0.62	0.90	
Right	3.50±0.58	3.10±0.64	0.02	
			OR	95% CI
Multiple vessel disease	28%	73%	0.15	0.15,0.46
Lesions non-CCA stenosis >20%	36%	78%	0.2	0.1,0.5
CCA Residual** stenosis <100%	81%	73%	0.25	0.1,1.2
Multiple lesions CCA stenosis >20%	14%	39%	0.3	0.1,0.9

CCA = culprit coronary artery; CI = confidence interval; LAD =left anterior descending; LCx = left circumflex: LMS = left main stem; OR = odds ratio; * = data are presented as mean ± standard deviation; ** = after non - mechanical reperfusion.

The severity of the stenosis of the diseased non-culprit coronary arteries as well as the presence of multiple lesions in these vessels was also significantly higher in the sedentary group. The residual stenosis of the culprit coronary artery after non-mechanical reperfusion was determined in 29 vessels of the sport group and in 26 vessels of the sedentary group.

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Among sporting people there was a tendency to show less severe residual stenoses. The number of multiple lesions of the culprit artery was significantly lower in the sporting group. The distribution of vessel dominance between the two groups was not different. Collateral filling was demonstrated in almost 50% of (sub)occluded culprit coronary arteries of both groups. There was grade III collateral filling in 60% of these vessels. The distribution of the site of the lesion in the culprit artery was almost the same in both groups (proximal in 60; mid in 9; distal in 3). Determination of the lesion morphology of the culprit arteries showed a similar high prevalence (>65%) of eccentric lesions in both groups. Thrombi were detected in 30 culprit arteries with a similar incidence in both groups.

Follow-up. After a mean follow-up of 24 months (range 6-62), the occurrence of new coronary events and the necessity for coronary angioplasty and coronary bypass surgery was more frequent in the control group (N=10) as compared to the sporting group (N=6). Repeat coronary angiographic study in almost 50% of patients of both groups showed that re-stenosis (40% to 70%) of the culprit coronary artery, as well as the development or increase of obstructive disease (40% to 100%) in other vessels, was more frequent in the control group (12 vs 6). Two to three months after their discharge from hospital, 18 non-surgical patients of the sporting group partially or fully had resumed their previous sporting activities. All but one of these patients remained in good health during follow-up.

DISCUSSION

This study demonstrates a common pathogenesis for the occurrence of acute coronary syndromes related and unrelated to sport and shows that sporting people have a different clinical and coronary angiographic profile compared to sedentary people. Sporting people had fewer coronary risk factors and less extent and severity of coronary artery disease. Moreover, the observations in this study are consistent with a better acute and long term outcome with regard to survival, recurrence of coronary events, need for revascularization procedures and development and progression of coronary artery disease among the sporting population. Previous studies have demonstrated that habitual physical activity has a favourable influence on coronary risk factors and coronary death (12-18,48-52). Exertion and its

protective effects can be partially related to self-selection of subjects for a healthy vigorous life style. In this context it is noteworthy that 50% of the sportsmen in this study did not smoke and that those who resumed sporting activities had a better long term outcome. Therefore self-selection may play a role but this appears to be inherent to the subjects themselves. On the other hand, fewer risk factors, or even their absence, did not preserve these people from an acute coronary event. Our findings support the view that regular exercise does not prevent but significantly reduces the extent, severity and progression of coronary artery disease. Severe multivessel disease has also been detected in endurance runners (21,53). Coronary disease can be regarded as an age related phenomenon in middle-aged people with at least one coronary risk factor, or when no other cause is known (21,29-32,53,54).

This study raises the question as to whether, in view of the different characteristics, the pathophysiology of acute coronary syndromes related and unrelated to sport is also different. It is well known that most acute coronary syndromes occur at rest. Is the relationship between sporting activities and coronary events a mere coincidence? In numerous studies a considerable percentage of all coronary accidents and sudden deaths have been reported as occurring in direct relationship with moderate and high level physical activity (20-34,53-54).

According to the present analysis, sporting and sedentary people share common findings concerning the ischemia related coronary artery, such as the presence of thrombus, site and morphology of lesions, which indicate a common pathogenesis (plaque rupture) for coronary (sub)occlusion. There is ample clinical and pathological evidence that the acute coronary syndromes are the manifestation of dynamic intra-coronary processes which result from the rupture or fissuring of an atherosclerotic plaque (35-37). Plaque rupture can lead to coronary (sub)occlusion through intimal haemorrhage and luminal thrombosis (37). The factors responsible for plaque rupture remain elusive, but are related to a circadian rhythm depending on neurohormonal physiologic changes, which in turn could influence haemodynamic forces on site (35,41,42). With regard to physical activity, there is no direct evidence that exercise can precipitate plaque rupture. Exercise is associa-

ted with a substantial rise in serum catecholamines and with increased platelet count and activation (55-57). Catecholamines as well as platelets can induce vasoconstriction of a diseased segment of a coronary artery; the former by unopposed α-adrenergic stimulation due to endothelial dysfunction, the latter by releasing thromboxane A2 and serotonin after adherence to an atherosclerotic plaque (58-60). Therefore, it can be hypothesized that exercise-induced vasoconstriction may be the trigger responsible for plaque rupture (33,34,58,59). Although the pathogenesis of acute coronary events related and unrelated to physical exertion appears to be the same, the precipitating factor(s) and the mechanism(s) envolved may be different for exertion-related events.

The present study presents a number of arguments in favour of a cause-effect relationship between sporting activities and the occurrence of an acute coronary event. Firstly, the group of sportsmen clinically represents a very different population to that of sedentary people. Secondly, in the majority of these patients the absence of prodromal symptoms denoted the suddenness and unpredictability of the coronary event. Moreover, the time of which the ischemic coronary event occurred did not follow a circadian pattern but was clearly related to a normal individually predetermined exercise time. Therefore, as was suggested by previous studies, the peculiarity of being activity-related events should not be regarded as being merely coincidental (20-34).

It has already been reported that endurance vigorous exercise both protects against coronary artery disease and is a potential provoker of acute coronary syndromes (27) but the reason for the susceptibility of some conditioned people to develop a coronary event in relation to exercise remains unsettled.

The generalizability of the results of the present study is limited by the selection of the patients studied and may not apply to a population of occasional and uncoditioned and not previously healthy sporters.

The findings of this study define the coronary benefits and risks of sporting activities that relate to the occurrence of acute coronary syndromes. Our data indicate that, whilst endurance exercise is associated with less coronary artery disease, vigorous exertion itself can precipitate an acute

coronary event. **Acknowledgement**. We greatly appreciate the secretarial assistance of Mrs Lilian Brons and Mrs Mary Cragg.

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CHAPTER 8

GENERAL DISCUSSION

In this thesis the role of physical exertion on the development and manifestation of atherosclerotic coronary artery disease and sudden cardiac ischemic death was investigated in previously healthy well conditioned people and in patients with coronary artery disease. This study shows the first clinical and angiographic demonstration of a continuous spectrum of acute coronary syndromes related to exertion and provides the largest series of acute coronary angiographic findings in resuscitated victims of sudden cardiac ischemic death. In the following paragraphs some final general comments will be made and the main limitations of the study together with the recommandations for areas of future investigation will be indicated. At the end a hypothesis will be presented suggesting a haemodynamic mechanism for the development of exercise-related acute coronary syndromes.

Study group composition.

Numerous previous studies have reported on small or large series of sudden deaths related to sport (1-21). In some cases only the diagnosis of acute myocardial infarction could be made either before sudden death occurred or after successful resuscitation (10,14,18,21-32). In the majority of reported series the main cause of sudden death was attributed to obstructive coronary artery disease. However, in the vast majority of instances the diagnosis was made a posteriori on the basis of necropsy findings. It is not known how often the diagnosis of coronary or cardiac death was made only because no other abnormalities were found. Therefore, a causal relation between the necropsy findings and the suspected cause of death was thought highly probable but could never be demonstrated. This factor of uncertainty led to various speculations about the mechanism of these deaths. Furthermore, the majority of these victims of sudden death were either unconditioned people who started sporting at middle age or well conditioned but exercising only for a few years. The level of physical

exercise very often was not mentioned, nor whether exercise was habitual. A considerable number of patients were known with cardiac disease or previous myocardial infarction, or other systemic diseases.

This study, in order to avoid confounding variables, was designed to investigate a specific population of well conditioned habitually sportive healthy people who had exercised more or less continuously since their youth. This population is believed to represent the ideal example of healthy life style, with a lower incidence of coronary artery disease and death. It was this population who survived unstable angina, acute myocardial infarction and cardiac arrest that constituted the main part of this study. Clinical and laboratory data could therefore be obtained without uncertainty in these patients. Furthermore, coronary angiographic study, in most cases in the acute stage, was performed in all patients. This provided detailed information of their coronary status and identified the artery responsible for the ischemic event. The high selection of this study limited the number of subjects included. It was further attempted to gather and analyse the clinical and coronary angiographic findings of unexpected acute coronary ischemic events occurring during or directly after a supervised exercise stress test. These in-hopital findings were compared with those of out-of-hospital events in order to achieve a better insight into the mechanisms of exercise-related acute coronary syndromes. Finally comparing a group of conditioned people with a group of sedentary people (with regard to the occurrence of an acute coronary event related to sport or at rest) it was attempted to identify differences or similarities, and peculiarities or characteristics which could elucidate the development of coronary artery disease and the pathogenesis of acute coronary events in relation to exertion, and identify subjects at risk for such an event.

Causes and mechanisms of exercise-related sudden death.

The occurence of sudden death related to moderate and heavy exertion has been attributed to various cardiac and non cardiac causes, both in athletes and in physically active people.

Cardiac and non-cardiac causes. Myocarditis, idiopathic hypertrophic

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obstructive and non-obstructive cardiomyopathy, congenital anomalies of the
heart or coronary arteries, rupture of the heart or the aorta, congenital
or acquired valvular disease, fibromuscular dysplasia of the sinus or
atrioventricular node artery, heart failure and heat stroke account for the
reported causes of death during exercise not associated with obstructive-
atherosclerotic coronary artery disease (19,33-38). In one occasion
unilateral absence of kidney and subarachnoid haemorrhage have also been
reported (7). The mural left anterior descending coronary artery has also
been implicated in sudden exertional death : in one case of acute myocardi-
al infarction in a 20-year-old national-class swimmer during training swim
(39-40) and in one case of ventricular fibrillation in a 15-year-old
professional soccer player (40A). A woman resuscitated from ventricular
fibrillation during a session of ''aerobic''dancing was found to have a
myxomatous mitral valve with prolapse (41). Taken overall, exercise-related
mortality in patients younger than 35 years of age is mainly due to non-
atherosclerotic coronary artery disease (17). The proposed mechanisms
responsible for these deaths have generally been accepted as more or less
evident.

Silent ischemia. The reported studies also indicate that victims of sudden
death due to causes other than coronary artery disease are not likely to be
successfully resuscitated. Conversely, the vast majority of survivors of
out-of-hospital cardiac arrest show obstructive coronary artery disease
(42). Because acute myocardial infarction is not always present in survi-
vors of cardiac arrest, silent ischemia has been proposed as a possible
mechanism. Silent ischemia was detected in a large number of survivors of
cardiac arrest (42). However, this finding does not differentiate survivors
of exertion - and nonexertion-related cardiac arrest (42). The concept of
silent ischemia implies the preexistence of severe coronary artery disease.
However even though severe disease is present the provocation of silent
ischemia during exercise testing is generally not associated with life
threatning arrhythmias (42-44). It is probable that the occurrence of
silent ischemia in the presence of a stable coronary lesion may not be
sufficient to cause cardiac arrest. On the contrary, silent ischemia as a

result of acute impairement of coronary flow can have more profound haemodynamic effects and provoke electrical instability. A significantly higher incidence of exercise-induced ventricular arrhythmias was observed in survivors of cardiac arrest with three vessel coronary artery disease and compromised left ventricular function (45). However it is unlikely that this population would engage in haevy physical exercise.

Arrhythmias and metabolism. The occurrence of sudden death in relation to sporting activities has often been explained by cardiac arrhythmias. Accelerated idioventricular rhythm as well as first and second degree atrioventricular block is seen frequently in trained athletes and are of no prognostic importance (46,47). During exercise, ventricular arrhythmias as ectopic beats, couplets and salvos are apparently not more frequent among healthy athletes and conditioned people than in healthy sedentary people (48,49). However the development and nature of rhythm disturbances may be different in subjects with coronary artery disease (45,50). Metabolic and neurohumoral influences associated with exercise may precipitate or contribute to an arrhythmia. The rise in serum catecholamines associated with sporting activity may cause myocardial ischemia and arrhythmias (45,51). Plasma potassium increase during exercise has also been implicated as a cause of arrhythmias (52). Furthermore, high catecholamine levels may remain elevated after exercise (53) and may interact with the correspondingly increased free fatty acids to produce arrhythmias and thrombosis in patients with severe obstructive coronary artery disease (54-56). Such a mechanism may be responsible for sudden death after exercise. Smoking by increasing serum free fatty acids and catecholamines may play an additional role in the genesis of arrhythmias (57,58). However these hypotheses have never been confirmed in a clinical setting. In one study it was demonstrated that a high concentration of circulating free fatty acids is not implicated in the genesis of arrhythmias in experimental myocardial infarction (59).

Other mechanisms. Thermal stress, such as taking a hot shower after exercise, may also result in increased heart rate and arrhythmias (60). The

hypothesis is that increased venous pooling in the muscles and skin may cause a diminished cardiac return and myocardial ischemia (60). Hyperpy-rexia and heat stroke, observed in runners not taking adequate amount of water during marathon running, can cause localized sub-endocardial necrosis (61-63). Occasionally the ''trauma'' caused by a football on the chest in experienced soccer players has been indicated as the cause of acute myocardial infarction and sudden death (26-30).

Coronary sclerosis. Although aforementioned hypothetical mechanisms can explain the occurrence of a number of deaths, there is pathological evidence of severe stenosis or occlusion of at least one major coronary artery in the majority of victims of sudden death associated with sporting activities (1-18). A controversial observation consists with the finding of no important or even no evident obstructive coronary disease in some young survivors of exercise related myocardial infarction and sudden death (24,25,28,30,31). A similar finding has often been reported in young patients after myocardial infarction (64). It is regrettable that in these cases the lack of analysis of the circumstances surrounding acute myocardi-al infarction does not allow us to make any comparison or conclusion. Reasonably, acute myocardial infarction and acute ischemia can be regarded as the most likely cause of sudden death when it occurs during of directly after vigorous exercise (65-68). Large epidemiologic and pathologic studies support this view (16,65-70). When pathological examination of the coronary arteries was performed, this showed either fresh sub-occlusive thrombus or acute intimal lesion in 15% to 80% of cases (1-18,70-75). This discrepancy is amply explained by the different techniques used at necropsy studies.

Coronary spasm. Alternatively exercise-related coronary spasm has been postulated to cause temporary occlusion of those coronary arteries that appeared patent and free of thrombi at postmortem examination. Therefore, it was suggested that reperfusion of previously ischemic areas after relief of coronary spasm caused cardiac arrest. Although this mechanism remains hypothetical, coronary spasm has been demonstrated during exercise testing in patients with coronary artery disease and in patients with variant

angina (76-78). However, the occurrence of coronary spasm and myocardial ischemia in this setting is generally not associated with cardiac arrhythmias (76). Coronary spasm has also been implicated as the etiologic factor in some cases of sudden death, but it is still controversial whether its role in unstable angina and acute myocardial infarction is primary or secondary, or both (79). There is evidence that coronary spasm can occur as a result of release of thromboxane A2 and serotonin after activation of platelets (80-82) as in the case of intimal disruption – a common pathological finding in patients who died after unstable angina and acute myocardial infarction (83-85).

Platelets and haemostasis. It has been demonstrated that exercise influences factors important for the inibition and initiation of thrombosis. One of the relevant haemostatic factors is platelet activity. Platelets may be activated after adherence to an atherosclerotic plaque thereby releasing thromboxane A2 and serotonin (81). By consequence a reduction of the coronary lumen can occur by mechanical obstruction and by induction of vasoconstriction. Exercise has also been demonstrated to induce platelet activation in young survivors of exercise-related myocardial infarction (86). Platelet count, adhesion and aggregation can increase in patients with exercise-induced myocardial ischemia (87-89). Controversially platelet aggregability can be inhibited by moderate-intesity physical exercise in overweight men (90). Fibrinolysis, measured as decrease of plasminogen activator inhibitor, increased in sporters and in people engaged in a training program as compared to inactive people (91-93). The increased fibrinolysis was more manifest in people who stopped smoking and lost weight during the training period (93). However, although fibrinolysis increased no systemic effects could be measured (91). The increased fibrinolytic activity may theoretically help to prevent thrombotic processes. However, this may not be the case in acute coronary events when endothelial disruption activates a coagulation cascade which can annullate both the intrinsic and the enhanced fibrinolytic activity induced by exercise (94-96). From a clinical therapeutical angiographic, angioscopic and pathological point of view thrombosis is the predominant finding in

unstable angina, acute myocardial infarction and sudden ischemic death (83-85,95-99). Thrombosis plays a predominant role in acute coronary (sub) occlusion.

Plaque rupture. Plaque fissuring or rupture with a variable degree of intimal haemorrhage and luminal thrombosis and periferal embolisation is a common finding in patients with unstable angina and acute myocardial infarction who died suddenly (98). Angiographic and angioscopic studies in patients with unstable angina and acute myocardial infarction consistently showed the presence of ruptured plaques with intraluminal thrombosis (97-99). Plaque rupture is being considered as the pathological substrate for the initiation and progression of the acute coronary syndromes. With regard to sudden death early spontaneous coronary recanalization may explain the absence of occlusive thrombus in all cases examined postmortem. However it is possible that the arterial segment corresponding to the plaque rupture develops occlusive spasm in response to vasoconstrictor substances released by intraluminal and intraintimal thrombus formation. Therefore postmortem relief of spasm may also be invoked to explain the absence of total occlusion. Self-limiting plaque rupture with mural thrombus has also been found in 10% of non-cardiac victims of sudden death indicating that this alteration can be quite frequent in the general population (84). The mechanisms responsible for the initiation of plaque rupture are still speculative (100). A circadian variability has been demonstrated for the occurrence of acute myocardial infarction and sudden death probably reflecting a physiological increase of fibrinogen, catecholamines and platelet aggregability (101-2). These physiologic changes can increase the chance of rupture of an atherosclerotic plaque. The structure and chemical composition of the plaque may also play a role (100). Overall, in view of the rhytmic motion, smooth muscle tone, distending pressure and neurohormo-nal physiologic changes to which the coronary arteries are continuously subjected, it is not surprising that plaque rupture may occur at the place of atherosclerotic segments (100). Strenous exercise is expected to enhance most of (if not all) the above mentioned factors thereby increasing the possibility of plaque rupture. Furthermore numerous epidemiologic studies

indicate that the occurrence of exercise-related sudden death does not follow a circadian rhythm suggesting a causal relation between exertion and cardiac arrest (16,67-69).

Value and limitations of the present study

Observational and epidemioligic studies have had the merit to focus on the phenomenon of coronary artery disease and coronary death related to exercise. It was stated that a significantly increased risk of death was associated with exertion in middle aged men and especially in the unfit. Numerous reports have further focused on the occurrence of sudden death in relation to sport and indicated coronary artery disease as the main finding and most probable cause of death. The presumed explanations regarding the mechanism(s) by which exertion can induce or precipitate sudden death remain in many aspects hypothetical and speculative (1-18,67-69). Further-more the precise role of (regular) exercise in the development and manife-station of coronary artery disease still remains undefined.

This study demonstrates in the first place that exertion can be associated with sudden death, acute myocardial infarction and unstable angina. It was also shown that these three clinical acute coronary syndromes can occur during exercise as well as within one hour after it. The time delay of one hour after exercise is arbitrary but considered to maintain the association with the coronary event (103). Furthermore a relation between exercise and acute coronary events was demonstrated in previously healthy subjects as well as in patients with known or suspected coronary artery disease.

A series of new observations can be derived from the analysis of the findings and data achieved with this study. An acute coronary event related to sport is in most cases unexpected. Although also in the general popula-tion such an event is very often unexpected, prodromal symptoms in exerci-sers were significantly less frequent. One could observe that sporters often deny their symptoms. Because of the lack of prodromal symptons such an event can also be considered as unpredictable. In the cases reported in relation to exercise testing the development of a coronary event was also unexpected but not unpredictable in every case.

In this study the coronary artery responsible for the acute event was identified. Further, it was shown that in almost 25% of the culprit arteries, after non-mechanical reperfusion, there was a minor to moderate residual stenosis. Clinically, such a degree of obstructive disease is not expected to provoke ischemia and symptoms. The lack to show angiographically a minor stenosis in a higher percentage of cases can rely on persistence of intracoronary thrombi or intimal haemorrhage (84). Nevertheless in sporters the degree of residual stenosis of the culprit artery was less than that found in an age-matched group of sedentary people. The low percentage of prodromal symptoms can relate to the finding of minor residual stenosis of the culprit artery and lead to the conclusion that exercise can induce abrupt (sub)occlusion of a previously moderately diseased coronary artery. A clinical demonstration of this occurrence was made possible in a few patients after an exercise stress test. These findings also support the initial hypothesis of a causal relation between sport and acute coronary events. Although the questions of why that day and why at that time a coronary event occurred remain unanswered, the relation of these events to exertion was direct and indicated a causal relationship. In other studies a statistical analysis of these events showed that they occurred in relation to exercise significantly more often than expected by chance. The recurrence of acute coronary events in relation to sport in two cases in this study demonstrates that the relation cannot be further regarded as merely coincidental.

This study also demonstrated that people engaged in regular sporting activities have less coronary risk factors and less extent and severity of coronary artery disease than their sedentary coetaneous companion. This shows that regular vigorous exertion protects against coronary atherosclerotic disease and death but does not render the subjects immune to them. Coronary artery disease can be reduced but not arrested by habitual physical exercise. In some previous reports it has been shown that obstructive coronary disease can even occur in highly trained people (18-22-32). This applies both for people with and without coronary risk factors as shown also in this study.

The present study provides the first acute coronary angiographic demonstra-

tion of a continuous spectrum of acute coronary events related and unrelated to sport. The coronary angiographic findings were similar and suggested a common pathogenesis. However although the pathogenesis is likely to be the same, the precipitating factor(s) (pathophysiology) may be active throughout other mechanisms in sport-related syndromes.

As far as sudden death is concerned this study showed that exercise-related cardiac arrest can rely on an acute coronary event, irrespective of the clinical presentation after resuscitation (unstable angina, acute myocardial infarction or no ischemia). It was demonstrated that exercise - related silent ischemia can precede cardiac arrest and that the electrocardiogram can be normal after restoration of the circulation. Therefore the diagnosis of sudden ischemic death may be missed in the presence of a normal electrocardiogram after resuscitation. In such circumstances coronary angiography is recommended. Conversely it was also demonstrated that no ischemia was detectable on the electrocardiogram just prior to the occurrence of exercise-related cardiac arrest and that acute ischemia was present after resuscitation. These two possible manifestations seem to depend on collateral filling of the culprit vessel subject to acute (sub) occlusion and probably related to the evolution of the acute lesion itself.

Sudden ischemic cardiac death. Some data of this study may also shed some more light on the mechanisms of cardiac arrest in acute transmural myocardial ischemia. In experimental studies it has been shown that both acute coronary occlusion and reperfusion can trigger the occurrence of ventricular fibrillation (105). The pathological finding of peripheral coronary thrombo-embolisation, with or without coronary occlusion, in victims of sudden ischemic death has been ascribed as a cause of ventricular arrhythmias and cardiac arrest (84,85-106-107). These obervations however are based on material of patients who died hours or days after the onset of acute myocardial infarction. Furthermore an undetermined series of postmortem changes can occur. In this study, in both the patients admitted with the diagnosis of acute myocardial infarction or as resuscitated from cardiac arrest there was acute transmural ischemia on the electrocardiogram. The predominant finding at acute coronary angiographic study was

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occlusion of the culprit artery. Patent vessels were found after prior administration of thrombolytic therapy. Other parameters such as vessel diameter and dominance, culprit coronary artery, site of occlusion, morphology of lesion and presence of thrombus were similar in patients with acute myocardial infarction and cardiac arrest, either in sporters and in sedentary people. Thus, no coronary angiographic differences were found in patients with acute myocardial infarction irrespective of the occurrence of cardiac arrest. Therefore it is not unreasonable to suggest that the development of cardiac arrest might just rely on enhanced individual myocardial instability. This electrical instability may be manifest during the episode of acute ischemia but may not be provocable at a later stage when ischemia is not present. Coronary occlusion, rather than reperfusion, seems the trigger responsible for sudden ischemic death.

Cerebral outcome after cardiac arrest. It is interesting to note the excellent cerebral recovery of all but one resuscitated victims of out-of-hospital cardiac arrest in this study. Although these patients were in coma on admission, after cardio-pulmonary resuscitation lasting approximately a mean of 20 minutes, they had a complete cerebral recovery. Besides this study the author and his colleagues had the same experience with a larger number of survivors of sudden ischemic death (108-110). A similar experience has also been recently reported by others (111). It is noteworthy that the single patient who died of cerebral complications did not receive thrombolytic theraphy. There is suggestive experimental evidence that early antithrombotic or thrombolytic therapy after resuscitation can promote post ischemic neuronal recover (112-113).

Limitations. In this study an attempt has been made to increase our understanding of the development and manifestation of coronary artery ischemic disease in relation to sporting activities. Therefore the subject of this study only represents a small part of the body of possible causes responsible for the phenomenon of exercise-related sudden death. The findings of coronary (sub)occlusion and the angiographic evidence of plaque rupture do not necessarily exclude other possibilities in the pathogenesis

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of an acute coronary event in the patients of this study. However, determination of the causal role of other factors (hydration, free fatty acids, hyperthermia, enhanced thrombosis etc.) is difficult and their precise role is still hypothetical. In the patients of this study there were no abnormalities detected on routine blood examination and basic haemostatic tests were normal. As regards to coronary artery diseases the observations made in this study might not necessarily apply to all cases of acute coronary syndromes related to exertion. Indeed the study selection comprised a group of well trained habitually sportive people (which has not been previously reported in the literature). Therefore the results presented may not apply to occasional, unconditioned and not previously healthy people developing an acute coronary syndrome related to sport. In this study and in previous reports by others it has been perhaps arbitrary to assume that events occurring (within one hour) after exertion still are related to it. Limiting the study group to coronary events occurring during exertion could avoid a series of confounding variables connected with the post-exercise period (thermal stress of hot shower, smoking and release of free fatty acids, emotional stress etc).

General conclusion. The three acute coronary syndromes, unstable angina, myocardial infarction and sudden death, can be associated with sport and have a common pathogenesis. Acute coronary syndromes related to sport can occur in previously healthy well conditioned young and middle-aged people with or without coronary risk factors. In this population the occurrence of an acute coronary event is very often unexpected and unpredictable. Sudden death related to exercise can be due to acute coronary (sub)occlusion also in cases that acute coronary envolvement is not clinically evident. A preexistent severe stenosis is not a prerequisite for developing an acute coronary event in relation to sport.

With regard to the culprit coronary artery in acute coronary syndromes there are no differences whether their occurrence is related or unrelated to sport. The basic pathologic coronary lesion is likely to be the same: plaque rupture. The precipitating factor may be different. In view of our findings the hypothesis of exercise-induced plaque rupture is at present

the most probable mechanism. People engaged in regular sporting activities belong to the healthy population, have less coronary risk factors and in case of coronary accidents have a more favourable clinical outcome. Regular exercise is associated with less severity and extent of atherosclerotic coronary artery disease and therefore has a coronary protective effect.

There is convincing evidence of a causal relationship between sport and acute coronary events. It remains unknown why some subjects are prone to develop such an event.

Areas of future research and recommendations. At present, the study of the phenomenon of sudden cardiac ischemic death and other coronary syndromes related to vigorous exertion is hampered by inadequate attention being paid to the problem by sports-governing bodies and by the relative indifference of physicians to the circumstances preceding the development of an acute coronary syndrome. A national registry of all coronary syndromes occurring during and directly after sporting activities is expected to result in the same limitations of previous reports and epidemiologic studies. Although a better insight might be provided into the real impact of sport on the provocation of coronary events this will not help to elucidate the mechanism(s) of these events nor help to indentify subjects at risk. The approach of performing (acute) coronary angiography in this study has proved to provide original and important information by means of which new light can be shed on the pathogenesis of exercise-related acute coronary events. Therefore, future studies should achieve all clinical and coronary angiographic data of sporting people developing a coronary syndrome.

In view of the low percentage of coronary events in the sporting population (in the Netherlands approximately 150 deaths per year. 113A) a prospective large-scale comparative study between sporting and non-physically active people is unlikely to be feasible, because of the organization needed and high costs requested. However it should be investigated whether an international cooperation could be able to organize and finance such a prospective study. Future observational and clinical studies should relate to clearly defined habitual exercisers or well conditioned people versus sedentary people. Attention should also be paid to the occurrence of acute coronary
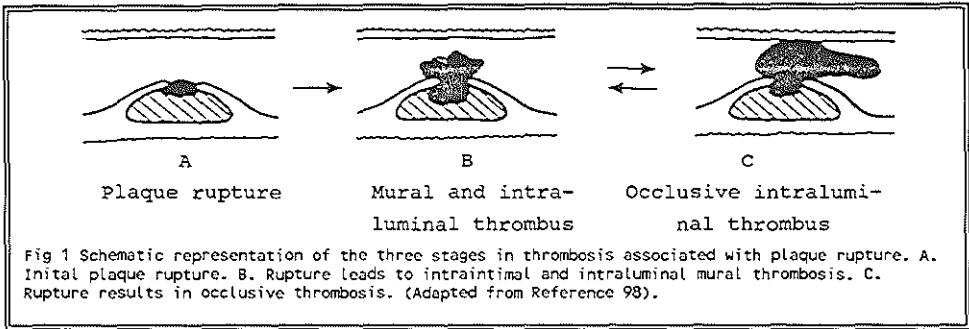
events unrelated to exercise in the sporting population.

The identification among sporting people of subjects at risk for a coronary event related to sport remains the main problem. Therefore, education about the kind of cardiac symptoms and their early recognition is of paramount importance for sporting people. A medical check-up should be mandatory for all individuals aged 30 years and older who intend to start sporting. An exercise stress testing should be routinely performed. Regular control should be required for those people with known coronary risk factors. Sporters should be encouraged to stop smoking and have hypertension and hypercholesterolemia treated. Survivors of myocardial infarction and sudden death related and unrelated to sport should undergo coronary angiography and heart catheterization prior to resume or initiate sporting activities. They should be advised by a sport-physician and a cardiologist both for competitive and recreational sporting activities. After resuming sport these people should be followed-up very carefully because of the possibility of recurrence.
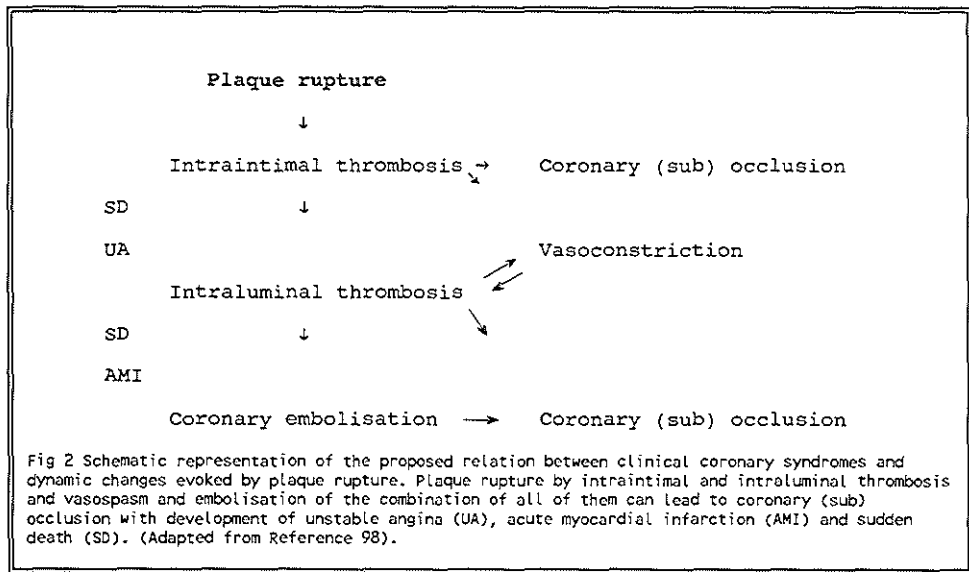
EXERCISE - INDUCED PLAQUE RUPTURE

A hemodynamic hypothesis

The basic lesion of atherosclerosis is the intimal plaque. Fissuring or rupture of an atherosclerotic plaque can lead to both progression of chronic atherosclerosis and episodes of acute coronary thrombosis with the potential development of acute ischemic syndromes (100). The concept that atherosclerotic plaques undergo rupture has been clearly defined by recent pathological, angiographic and angioscopic studies (97-99). Rupture is unlikely to occur only in severely obstructive plaques (98). Some angiographic studies in patients treated with thrombolytic therapy for acute myocardial infarction have shown that after reperfusion the underlying lesion had less than 70% diameter stenosis in the majority of cases (100). Furthermore coronary occlusion can occur at sites where the degree of preexisting stenosis is 50% or less of the vessel diameter - as it has been substantiated from necropsy and clinical studies in which angiograms taken some days or months before an acute coronary event were available (98,114, 117,118). The identification by postmortem angiograms of eccentric stenosis with ragged outlines and intraluminal filling defect consistent with plaque rupture and thrombus has drawn attention that identical appearances were present in angiograms of patients with unstable angina, acute myocardial infarction and in some resuscitated victims of sudden ischemic death (100,109,115,116). Therefore plaque rupture is considered as the pathological basis of the three acute coronary syndromes (98). Necropsy studies allowed the identification of three distinct stages in thrombosis associated with plaque rupture (Fig. 1). The first is an intimal tear with thrombotic mass (platelets) within the intima but without intraluminal thrombosis. The second is associated with a mural thrombotic component that projects out through the rupture into the arterial lumen. In the final stage the thrombus (mainly fibrin and red blood cells) within the lumen becomes occlusive. Mural non occlusive thrombosis are generally associated with distal emboli of small platelet thrombi (106,107).

Fig 1 Schematic representation of the three stages in thrombosis associated with plaque rupture. A. Inital plaque rupture. B. Rupture leads to intraintimal and intraluminal mural thrombosis. C. Rupture results in occlusive thrombosis. (Adapted from Reference 98).
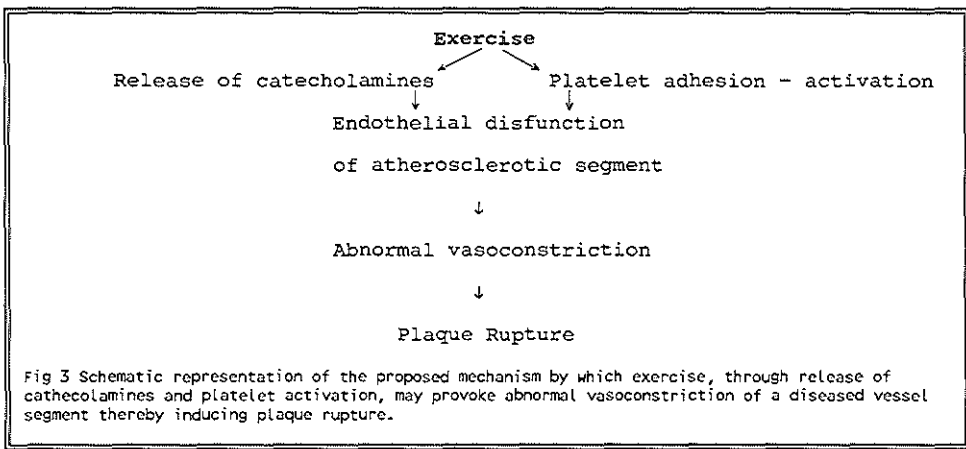
Such mural thrombi have also been observed by angioscopy in vivo in patients with unstable angina and at angiography in patients with unstable angina, acute myocardial infarction and survivors of sudden ischemic death (99,109,119,120). Platelet adhesion and thrombus formation by releasing vasoactive substances can induce coronary vasospasm which in turn can reduce coronary blood flow in situ and enhance the progression of thrombus formation (121-123). Rupture of an atherosclerotic plaque can initiate a series of hemostatic coagulative processes and dynamic vasoactive changes which can lead to coronary (sub) occlusion and the manifestation of an acute coronary event. (Fig. 2).

Fig 2 Schematic representation of the proposed relation between clinical coronary syndromes and dynamic changes evoked by plaque rupture. Plaque rupture by intraintimal and intraluminal thrombosis and vasospasm and embolisation of the combination of all of them can lead to coronary (sub) occlusion with development of unstable angina (UA), acute myocardial infarction (AMI) and sudden death (SD). (Adapted from Reference 98).

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The mechanism of plaque rupture is unknown. Pathological studies have revealed that atherosclerotic plaques are commonly composed of a crescent-shaped mass of lipids separated from the vessel lumen by a fibrous cap (98). The commonest site of tearing is where the cap is attached to the normal vessel wall and it seems that eccentric plaques are more likely to rupture (124-126). In a small proportion of intimal tears lipid pool was not involved. Computer modelling for analysis of simulated vessel walls containing plaques of different configuration and biochemical properties showed that a cap overlying an area of lipid pool is subjected to high concentration of stress which can contribute to intimal tearing (124). Beside structural and morphologic properties an increase of shear rate in the area of stenosis, anatomic changes of the vessel during each cardiac contraction and changes in coronary artery tone or pressure have also been suggested as possible factors that can lead to plaque rupture (100,126). Therefore the possibility of rupture of an atherosclerotic plaque may also depend on external mechanical influences. Moreover the above mentioned experimental model (124) can apply to plaques that clearly protrude into the vessel lumen but does not explain why rupture also occurs in moderately obstructive plaques (100). There is however additional evidence that atherosclerotic segments of coronary arteries have an abnormal vasodilator function, probably related to a deficiency in the production and release of endothelium – derived relaxing factor (127). In this regard the intracoro-nary administration of the vasodilator acetylcholine to patients with minor or severe obstructive disease resulted in vasoconstriction (128). Similarly diseased coronary arteries have impaired vasodilator responses to adenosine diphosphate as well as increased vasoconstrictor response to serotonin and thromboxane A_2 (129). Therefore it appears that atherosclerosis is associa-ted with an abnormal vasoconstrictor response to physiologically mediated neurohumoral stimuli. This abnormal response may be important in the pathogenesis of coronary vasospasm. Platelet adhesion and activitation at the site of damaged endothelium may play a contributing role by releasing vasoactive substances. Recent studies have also shown that cardiac sympa-thetic nerve stimulation by dynamic or isometric exercise can produce vasoconstriction of diseased coronary arteries (130-133). Exercise is
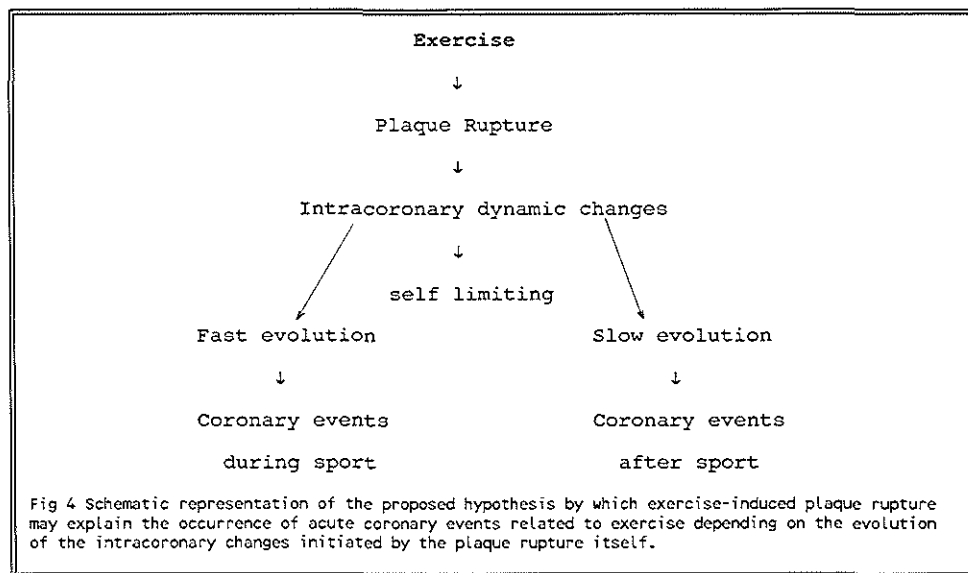
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associated with a rise in serum catecholamines (134) and in some patients the abnormal vasoconstrictory effect can be reduced or abolished by nitroglycerin (131) as well as by α-(135) and β- blockade (136). Unopposed α-adrenergic stimulation due to endothelial dysfunction of diseased vessel segments appears to be responsible for the abnormal vasoconstriction. During exercise the high rate of bending and twisting of the diseased coronary artery during each cardiac contraction and the related occurrence of vasoconstriction may enhance stress within the plaque creating conditions favourable for the development of plaque rupture. Intrinsic characteristics of the atherosclerotic lesion in combination with external hemodynamic mechanical forces acting on the plaque itself may contribute to its rupture. Therefore it is not unreasonable to hypothesize that exercise may induce rupture of an atherosclerotic plaque with the potential of developing coronary (sub) occlusion and the clinical manifestation of one of the acute coronary syndromes (Fig. 3).

Fig 3 Schematic representation of the proposed mechanism by which exercise, through release of cathecolamines and platelet activation, may provoke abnormal vasoconstriction of a diseased vessel segment thereby inducing plaque rupture.

This hypothesis can explain the suddenness of coronary events during or after exercise, the paradox of these events, the clinical presentation and the coronary angiographic findings of the patients described in this thesis. Such a mechanism may also explain why rupture occurs in moderate relatively nonprotruding plaques. This hypothesis may also give a rationale for the occurrence of coronary events either during or after exercise. If

exercise induces or provokes plaque rupture, the intracoronary dynamic changes set in motion can be either self-limiting or have a fast or relatively slow evolution. The rate of evolution of these intracoronary changes can explain respectively the occurrence of a coronary event during and after sport (Fig. 4).

Fig 4 Schematic representation of the proposed hypothesis by which exercise-induced plaque rupture may explain the occurrence of acute coronary events related to exercise depending on the evolution of the intracoronary changes initiated by the plaque rupture itself.

At present there is no direct evidence that hemodynamic forces or stimuli related to exercise can provoke plaque rupture. Therefore, this hypothesis and the proposed mechanism are speculative. Intensive clinical and experimental investigation in this area is necessary.

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SUMMARY

Acute ischemic coronary disease is the major cause of death in Western Civilization. A considerable number of sudden deaths and coronary events have been related to sporting activities. However, the mechanism of these deaths and events is still elusive.

In Chapter 3 a group of subjects with acute myocardial infarction and a group of subjects resuscitated from sudden death occurring after sport were studied. Their clinical and coronary angiographic data, together with the morphological analysis of the culprit coronary artery, suggested that the findings of both groups and, by consequence, the pathogenesis of their coronary events, were similar. It was further concluded that exercise might provoke coronary (sub)occlusion by inducing rupture of an atherosclerotic plaque. However, it could not be excluded that the occurrence of myocardial infarction and sudden death was merely coincidental. Two subjects were described who developed respectively recurrent acute myocardial infarction and sudden death after sport, and recurrent acute myocardial infarction during sport. These cases showed that some subjects are susceptible to developing a coronary event in association with exertion and that the association may not be merely coincidental.

In Chapter 4 the clinical, electrocardiographic and angiographic findings are reported of seven subjects who developed an acute coronary event after an exercise test which was normal in six cases. In four patients coronary angiography prior to the test showed either minor or no evident obstruction of the coronary artery, which appeared totally or sub-totally occluded after the test. This finding suggested that exercise induced plaque rupture, which in turn led to coronary (sub)occlusion. The time delay between ending a normal exercise test and the development of symptoms could also be explained by a delay in the terminal evolution of a coronary process initiated by plaque rupture. The findings concerning one of these subjects were extensively described in a case report. Another observation was that development of an acute coronary event with coronary (sub)occlusion is not necessarily related to pre-existent severe obstructive disease of

the coronary artery.

In Chapter 5 the question was addressed as to whether there were comparable findings among 42 middle-aged subjects who developed unstable angina, acute myocardial infarction and sudden ischemic death either during or after sport. The second question referred to the pathogenesis of these events. The third question was whether subjects at risk could be identified. Most subjects had no prodromal symptoms. Almost one third had no coronary risk factors. Acute coronary angiographic study showed similar findings among subjects with differing coronary events either during or after sport, suggesting a common pathogenesis. The lack of differences between acute myocardial infarction and sudden ischemic death (coronary occlusion was the most common finding) did not support the view that reperfusion arrhythmias were the cause of sudden death. Since in most instances the coronary event was unexpected and unpredictable, it was deduced that identification of subjects at risk might be possible, though very difficult. About 75% of subjects had single-vessel coronary disease and more than 38% showed a minor to moderate (up to 65%) residual stenosis after reperfusion of occluded coronary arteries. This latter finding integrated the conclusion drawn in Chapter 4 that a minor stenosis can constitute the basis for (sub)total coronary occlusion. Exercise-precipitated plaque rupture was indicated as the probable mechanism of the acute coronary events.

In Chapter 6 a comparison between sudden ischemic death occurring during or after sport and during or after an exercise test showed that exertion can precipitate sudden death by provoking an acute coronary event. It was also demonstrated that the clinical manifestation of sudden death can rely on silent ischemia, unstable angina and acute myocardial infarction. These differences depended on the process responsible for (sub)complete interrup-tion of flow and the presence of collateral circulation of the coronary artery involved. Arrhythmia deriving from acute temporary or persistent ischemia due to an acute coronary event rather than reperfusion was the cause of sudden death.

In Chapter 7 relevant clinical and coronary angiographic differences were shown between conditioned and sedentary people developing an acute coronary syndrome related and unrelated to exertion. Sporting people had fewer

coronary risk factors, extent and severity of coronary artery disease and a better short-and long-term clinical outcome. Analysis of the culprit coronary artery did not show differences between the groups. This indicated a common pathogenesis for acute coronary syndromes related and unrelated to sport. However the precipitating mechanism(s) may be different for sport related events. This comparison defined the benefits and risks of exercise and underlined the paradox of exercise unexpectedly causing an acute coronary syndrome in previously healthy people. Identification of subjects at risk does not seem to be easily achievable.

SAMENVATTING

Acute coronaire hartziekte is de belangrijkste doodsoorzaak in de westerse landen. Een beduidend aantal van plotselinge doden en acute coronaire hartziekten werd in verband gebracht met sportbeoefening, alhoewel het mechanisme van het overlijden en de coronaire ziekten hypothetisch blijft. In dit onderzoek zijn nieuwe waarnemingen van de klinische en acute coronaire angiografische bevindingen van gezonde goed getrainde mensen en van patienten beschreven die onstabiele angina pectoris of een hartinfarct doormaakten, of geresusciteerd werden wegens cardiale dood ontstaan respectievelijk tijdens of na het sporten en tijdens of na een inspannings- onderzoek. Er werd aangetoond dat de bevindingen bij deze mensen en patienten overeen kwamen. Het meest waarschijnlijke mechanisme voor de acute coronaire episodes was een door inspanninggeinduceerde ruptuur van een atherosclerotische plaque. (Hoofdstukken 3,5). Dit wordt ondersteund door de bevinding dat lichamelijke inspanning (sub)occlusie van een van tevoren normaal of matig stenotisch coronaire vaten kan veroorzaken (Hoofdstukken 4,5). Verder werd aangetoond dat plotselinge dood bij fysieke activiteit kan worden veroorzaakt door ventriculaire ritmestoornissen op grond van door inspanning geïnduceerde myocard ischemie (Hoofdstuk 6). Tenslotte (Hoofdstuk 7), sportbeoefenaars hadden minder coronaire risico factoren en minder ernstige coronaire vaatziekte. Voor aan sport en niet aan sport gebonden acute coronaire hartziekte geldt dezelfde pathogenese. De luxerende factor kan evenwel verschillen. Het ontstaan van een acuut

coronair syndroom in relatie tot sportbeoefening blijft in de meeste
gevallen onverwacht en onvoorspelbaar.

SOMMARIO

Le malattie coronariche acute (angina instabile, infarto acuto e morte
instantanea - le cosidette sindromi coronariche acute) rappresentano la
principale causa di morte nelle nazioni occidentali. Una percentuale
importante di morti e di malattie coronariche acute accade in relazione ad
attivita` sportive. Tuttavia il meccanismo responsabile di queste sindromi
coronariche acute non è ancora ben chiarificato. Questo studio riporta
nuove osservazioni cliniche e coronarico angiografiche di soggetti sani e
sportivi e di pazienti con sindromi coronariche acute occorrenti rispetti-
vamente in relazione ad attività sportive e ad una prova da sforzo. Si è
dimostrato che le caratteristiche coronarico-angiografiche di questi
soggetti e pazienti sono simili. Inoltre si è ipotizzato che l`esercizio
fisico possa provocare la rottura di una placca aterosclerotica inducendo
così una delle sindromi coronariche acute (Capitoli 3,5). Questa ipotesi
viene rafforzata dall`osservazione che l`esercizio fisico può provocare
l`occlusione di arterie coronariche precedentemente normali o moderatamente
stenotiche (Capitoli 4,5). In riguardo alla morte instantanea associata
allo sforzo fisico si è dimostrato che questa può essere causata da
disturbi ritmici ventricolari dovuti a ischemia miocardica. Quest` ultima
può risultare da occlusione coronarica acuta provocata dell`esercizio
stesso (Capitolo 6). Infine (Capitolo 7), i benefici dell`esercizio sono
stati definiti in contrapposizione al rischio paradossale dell`esercizio di
provocare una sindrome coronarica acuta. Soggetti fisicamente attivi hanno
meno fattori di rischio coronarico (colesterolo, uso di tabacco, ipertensi-
one) e numero e grado di stenosi coronarica inferiori rispetto ai soggetti
sedentari. La patogenesi (sviluppo) delle malattie coronariche acute in
relazione all`esercizio o a riposo e` la medesima. Tuttavia la causa può`
essere diversa nel caso di attivita` fisica. L`occorrenza della morte
instantanea, infarto acuto e angina instabile in relazione all`esercizio
fisico rimane nella maggioranza dei casi inaspettata e imprevedibile.

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