Left ventricular dilatation and neurohumoral activation as arrhythmogenic factors in myocardial infarction
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CHAPTER 1. Introduction

§ 1. General introduction

In 1859, Einbrodt demonstrated that vagal nerve stimulation could prevent ventricular fibrillation in the canine ventricle.\(^1\) This finding was not appreciated until Kent et al.\(^2\) reproduced this experiment more than a century later. Other investigators showed that the antifibrillatory effect of vagal nerve stimulation could be attributed to an opposing effect on sympathetic neural input.\(^3\) This concept proved highly valuable in the setting of acute myocardial infarction; treatment with beta-receptor blockade appeared to reduce the occurrence of ventricular fibrillation and sudden cardiac death.\(^4\) However, once treatment with thrombolytic agents was applied, the additional effect of beta-blockade on mortality\(^5\) or early ventricular arrhythmias\(^6\) was less clear.

In the early 1980s, van Gilst et al.\(^7\) described a clear-cut reduction in duration and occurrence of ventricular fibrillation during reperfusion when the angiotensin-converting enzyme (ACE) inhibitor captopril was added to a Langendorff perfused rat heart, a model of ischemia and reperfusion. This effect was paralleled by a significant reduction of catecholamine overflow. Subsequent experiments\(^8,9\) strongly suggested that this blunted neurohumoral response to reperfusion played an important role in the reduction of reperfusion-related ventricular arrhythmias. In addition, ACE inhibition proved to reduce myocardial injury, another potentially anti-arrhythmogenic mechanism. Based on these results, obtained both in vitro and in vivo, the Captopril And Thrombolysis Study (CATS) was designed to investigate the effects of captopril in humans during thrombolytic therapy for acute myocardial infarction.

By that time, it had become clear that changes in morphology of the heart after myocardial infarction, also known as remodeling, could have important implications for the occurrence of late ventricular arrhythmias. White et al.\(^10\) demonstrated the powerful predictive value of left ventricular dilatation assessed 6 weeks after acute myocardial infarction for the occurrence of sudden cardiac death. Since modulating effects of captopril on left ventricular remodeling had been described,\(^11\) an indirect effect on late ventricular arrhythmias could be anticipated. Serial echocardiography, which was part of the CATS protocol, allowed a more detailed evaluation of this possibly arrhythmogenic factor up to one year after myocardial infarction.

In this thesis, the main results of the CATS study are described with special interest in the effects of ACE inhibition on the occurrence of early and late postinfarction ventricular arrhythmias. In addition, the associations between
dilatation of the heart, activation of neurohumoral systems, and ventricular arrhythmias are evaluated in detail. Finally, noninvasive techniques, including body surface mapping and signal-averaged electrocardiography, are used to identify possible underlying electrophysiological mechanisms of the relation between dilatation and ventricular arrhythmias.

§ 2. Ventricular arrhythmias after thrombolytic therapy for acute myocardial infarction

In experimental research, ventricular arrhythmias are usually divided into acute, delayed, and chronic ventricular arrhythmias, each with different characteristics and mechanisms. In the acute phase, i.e., up to 2-4 hours after onset of myocardial infarction, ischemia is the predominant arrhythmogenic factor. Clinical arrhythmias equivalent to acute ventricular arrhythmias in the experi-

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Definitions used in this thesis

Ventricular arrhythmias include ventricular fibrillation (VF), ventricular tachycardia (VT), accelerated idioventricular rhythm (AIVR), uniform-, multiform-, and paired ventricular premature beats (VPBs), VPBs in bigeminy, and sudden cardiac death.

Early ventricular arrhythmias include ventricular arrhythmias occurring up to 48 hours after the onset of symptoms of acute myocardial infarction;
late ventricular arrhythmias refer to ventricular arrhythmias occurring later than 48 hours after the onset of myocardial infarction; the observation period in CATS was limited to one year.

Ventricular tachycardia is defined as a repetition of three or more VPBs with a rate exceeding 100 beats/min.
Sustained ventricular tachycardia includes VT lasting longer than 30 seconds or shorter when leading to hemodynamic collapse;
nonsustained ventricular tachycardia indicates VT with a duration shorter than 30 seconds, without a hemodynamic collapse.
AIVR is defined as a repetition of three or more uniform ventricular premature beats with a rate of less than 100 beats/min.
Pairs (paired VPBs) refers to a repetition of two ventricular premature beats.
High-grade ventricular arrhythmias include ventricular arrhythmias from Lown classes 4A and 4B (‘high Lown grade’) which are paired VPBs and sustained or nonsustained VT.
mental setting usually occur before patients reach the hospital. These arrhythmias are an important cause of sudden cardiac death, and consist mainly of ventricular fibrillation (VF). After the acute phase, the incidence of ventricular fibrillation drops, and other ventricular arrhythmias emerge, including ventricular tachycardia (VT) and accelerated idio-ventricular rhythm (AIVR). These arrhythmias occur up to 24-48 hours after the onset of myocardial infarction and are equivalent to the delayed ventricular arrhythmias found in the experimental setting, in which abnormal automaticity is the predominant electrophysiologic mechanism. Arrhythmias in this period also include the so-called reperfusion arrhythmias. Finally, late in-hospital ventricular arrhythmias and ventricular arrhythmias occurring after discharge are the clinical counterparts of chronic ventricular arrhythmias in the experimental setting, in which reentry is the predominant mechanism.

In this thesis, early ventricular arrhythmias are defined as ventricular arrhythmias occurring up to 48 hours after the onset of symptoms (‘CCU phase’). Late ventricular arrhythmias (‘late hospital phase’ and ‘chronic phase’) are defined as ventricular arrhythmias emerging after this period up to one year after myocardial infarction.

2.1. Early ventricular arrhythmias: role of reperfusion

When thrombolysis was considered for use in patients with acute myocardial infarction, there was serious concern about the possible occurrence of so-called reperfusion arrhythmias. This concern was based on numerous experimental studies which had shown a high incidence of VF when blood flow was restored to a previously ischemic part of the myocardium. Already in 1934, Tennant and Wiggers found VF in 10 out of 14 dogs upon reperfusion by release of a ligation of the left anterior descending coronary artery. Subsequent experimental animal studies in dogs and other species have also reported a high incidence of VF after sudden restoration of anterograde blood flow. By contrast, intermittent occlusion or gradual reperfusion both seem to result in a lower incidence of ventricular arrhythmias. In addition, the type of arrhythmia emerging upon reperfusion is largely dependent on the duration of the preceding ischemic episode. Battle et al. observed an increase in the incidence of VT and VF when the duration of ischemia was prolonged from 3-6 minutes to 30-45 minutes. However, Balke et al. observed a 67% reduction of ventricular arrhythmias when the ischemic period was extended from 30 to 60 minutes. De Graeff et al. noted only AIVR after a 60-minute occlusion period in their closed-chest pig model. The incidence of reperfusion-induced VF appears to be maximal after 20-30 minutes of ischemia, when both reversibly and irreversibly damaged
cells are present. After this period, life-threatening reperfusion arrhythmias are less likely to occur because the majority of cells in the infarcted region become necrotic.

Underlying mechanisms

The mechanisms leading to reperfusion arrhythmias are not fully understood. Rapid changes in potassium concentrations, $PcO_2$ and accumulation of calcium and lysophosphoglycerides next to increased adrenergic stimulation all appear to play an important role. The electrophysiological mechanism of these arrhythmias seems primarily nonreentrant in origin. In a study in the cat heart, Pogwizd et al. demonstrated that the initiating mechanism was nonreentrant in 75% of reperfusion-induced VT. In addition, these arrhythmias were maintained by a nonreentrant mechanism in 61% of cases. Likewise, during acceleration of sustained VT before transition to VF, nonreentrant mechanisms were operative.

Abnormal automaticity is especially noted in case of delayed reperfusion arrhythmias occurring several minutes after reperfusion. There is no direct evidence for triggered activity as a mechanism of reperfusion arrhythmias. However, the effect of calcium-channel blockers on reperfusion arrhythmias suggests a possible role of delayed afterdepolarizations (DADs). Delayed afterdepolarizations are especially seen in situations characterized by calcium overload and may result in triggered activity. Oscillations of the intracellular calcium concentration cause a transient inward current, which, if threshold is reached, can trigger one or more premature beats. Similarly, there is no conclusive evidence that early afterdepolarizations (EADs) play an important role in the occurrence of reperfusion arrhythmias. Early afterdepolarizations occur during the repolarization phase and are also capable of triggering ventricular arrhythmias if threshold is reached. Still, some investigators have reported the appearance of EADs upon reperfusion. Priori et al. reported a high incidence of EADs (54%) in cats upon reperfusion after a 10-minute period of ischemia. In this study, EADs were associated with the occurrence of reperfusion arrhythmias in 62% of cases.

In conclusion, most reperfusion arrhythmias are induced by a nonreentrant mechanism. This mechanism appears to be abnormal automaticity in most cases, although triggered activity, induced by DADs or EADs, may play a role.
INTRODUCTION

In the early 1980s, intracoronary thrombolysis was introduced as a new therapy for acute myocardial infarction. In a number of randomized and nonrandomized studies it was demonstrated that this therapy could safely be applied in humans, and that the incidence of life-threatening ventricular arrhythmias was low. In the study by Ganz et al., frequent ventricular premature beats, bigeminy, and AIVR were observed after infusion of intracoronary streptokinase. Only one patient required electrical cardioversion for VT; the average time from onset of symptoms to reperfusion was 4 hours. Goldberg et al. studied the incidence of reperfusion arrhythmias more extensively. In their study, reperfusion arrhythmias (mainly AIVR) were found in 82% of patients with successful thrombolysis. No VF was found in the first hours after restoration of flow. Goldberg et al. studied the incidence of reperfusion arrhythmias more extensively. In their study, reperfusion arrhythmias (mainly AIVR) were found in 82% of patients with successful thrombolysis. No VF was found in the first hours after restoration of flow. It should be noted that all of these patients were pretreated with lidocaine. The incidence of VF after thrombolytic therapy has been studied in a number of major thrombolysis studies.

Although these studies did not show a significant difference individually, an analysis of pooled data (Table 1.1) reveals a 13% reduction in the incidence of VF after thrombolytic therapy. In most of these studies, no distinction was made between VF during the acute phase of myocardial infarction or during the remaining in-hospital period. In a recent meta-analysis, the occurrence of early VF (up to 24 hours after myocardial infarction) in a number of major trials was evaluated separately. There proved to be no significant difference in the incidence of VF between patients treated with thrombolytic agents or placebo (about 3%) during this early period.

Table 1.1. Incidence of in-hospital VF in 5 major thrombolysis trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence of VF (treatment group)</th>
<th>Incidence of VF (placebo group)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI-1</td>
<td>388/5860 (6.6%)</td>
<td>439/5852 (7.5%)</td>
<td>0.88 (0.76 - 1.01)</td>
</tr>
<tr>
<td>ISIS-2</td>
<td>370/8592 (4.3%)</td>
<td>425/8595 (4.9%)</td>
<td>0.87 (0.76 - 1.00)</td>
</tr>
<tr>
<td>ASSET</td>
<td>94/2516 (3.7%)</td>
<td>116/2495 (4.6%)</td>
<td>0.80 (0.62 - 1.05)</td>
</tr>
<tr>
<td>AIMS</td>
<td>41/624 (6.6%)</td>
<td>46/634 (7.3%)</td>
<td>0.91 (0.61 - 1.37)</td>
</tr>
<tr>
<td>ISAM</td>
<td>37/859 (4.3%)</td>
<td>46/882 (5.2%)</td>
<td>0.83 (0.54 - 1.26)</td>
</tr>
<tr>
<td>Total</td>
<td>930/18451 (5.0%)</td>
<td>1072/18458 (5.8%)</td>
<td>0.87 (0.80 - 0.95)*</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; RR, risk ratio; VF, ventricular fibrillation. * Mantel-Haenzel risk ratio.

Incidence of reperfusion arrhythmias in man after the administration of thrombolytic therapy

In the early 1980s, intracoronary thrombolysis was introduced as a new therapy for acute myocardial infarction. In a number of randomized and nonrandomized studies it was demonstrated that this therapy could safely be applied in humans, and that the incidence of life-threatening ventricular arrhythmias was low. In the study by Ganz et al., frequent ventricular premature beats, bigeminy, and AIVR were observed after infusion of intracoronary streptokinase. Only one patient required electrical cardioversion for VT; the average time from onset of symptoms to reperfusion was 4 hours. Goldberg et al. studied the incidence of reperfusion arrhythmias more extensively. In their study, reperfusion arrhythmias (mainly AIVR) were found in 82% of patients with successful thrombolysis. No VF was found in the first hours after restoration of flow. It should be noted that all of these patients were pretreated with lidocaine. The incidence of VF after thrombolytic therapy has been studied in a number of major thrombolysis studies.

Although these studies did not show a significant difference individually, an analysis of pooled data (Table 1.1) reveals a 13% reduction in the incidence of VF after thrombolytic therapy. In most of these studies, no distinction was made between VF during the acute phase of myocardial infarction or during the remaining in-hospital period. In a recent meta-analysis, the occurrence of early VF (up to 24 hours after myocardial infarction) in a number of major trials was evaluated separately. There proved to be no significant difference in the incidence of VF between patients treated with thrombolytic agents or placebo (about 3%) during this early period.
As stated previously, the incidence of VF is especially high when reperfusion occurs after a relatively short episode of ischemia. Therefore, the effect of thrombolytic therapy administered shortly after onset of symptoms is of particular interest. Recently, the European Myocardial Infarction Project (EMIP) investigators\textsuperscript{40} studied the incidence of VF in 2750 patients receiving anistreplase 130 minutes after the onset of symptoms and before hospital admission. Ventricular fibrillation was significantly more frequent in patients receiving anistreplase (2.5% vs 1.6%). The authors suggested that this higher incidence of VF may have been related to early reperfusion. This finding has been disputed by others,\textsuperscript{41} who stated that VF related to cardiogenic shock or differences in concomitant medication (e.g., beta-blockers) may have obscured the relation between thrombolytic therapy and the incidence of VF. Other investigators using very early thrombolytic therapy within 1 or 2 hours after onset of symptoms\textsuperscript{42,43} have reported an incidence of VF similar to the placebo group of EMIP (1% or less). Thus, the increased incidence of VF after very early administration of thrombolytic therapy remains controversial.

One of the previously mentioned major thrombolysis trials, the Intravenous Streptokinase in Acute Myocardial infarction (ISAM) trial\textsuperscript{38} also reported on the incidence of ventricular arrhythmias other than VF in 1741 patients early after thrombolytic therapy. In this study, patients given streptokinase had more frequent ventricular premature beats (30.5% vs 19.4%, VPBs > 10/hour) and

\begin{table}[h]
\centering
\begin{tabular}{lcccc}
\hline
 & N & Duration (hrs) & VF (%) & VT (%) & AIVR (%) \\
\hline
Miller et al.\textsuperscript{46} & 39 & 12 & 5 & 90 & 90 \\
Cercek et al.\textsuperscript{45} & 45 & 24 & 0 & 85 & 90 \\
Gore et al.\textsuperscript{49} & 67 & 1.5 & 3 & 6 & 7 \\
Hackett et al.\textsuperscript{50} & 38 & 2.6 & 16 & 50 & 32 \\
Six et al.\textsuperscript{48} & 40 & \leq 4 & 4 & 26 & 23 \\
Zehender et al.\textsuperscript{51} & 30 & 24 & 10 & 80 & 77 \\
Gressin et al.\textsuperscript{47} & 40 & 24 & 3 & 80 & 88 \\
Heidbüchel et al.\textsuperscript{6} & 244 & 24 & 3 & 75 & 71 \\
CATS & 190 & 12 & 2 & 54 & 59 \\
All (range) & 733 & - & 3.6 (0-16) & 60 (6-90) & 60 (7-90) \\
\hline
\end{tabular}
\caption{Incidence of early ventricular arrhythmias after thrombolytic therapy using Holter monitoring}
\end{table}

AIVR indicates accelerated idioventricular rhythm; CATS, Captopril And Thrombolysis Study; VF, ventricular fibrillation; VT, ventricular tachycardia.
AIVR (5.4% vs 2.4%) than patients in the placebo group in the first 3 hours after thrombolytic therapy. The incidence of VT (3.8% vs 3.5%) was not significantly different. In the Western Washington intravenous streptokinase trial, VT was more frequent in the first 14 days after thrombolytic therapy (11.0% vs 4.5%). The incidence of early VT was not reported separately. Since continuous Holter monitoring was not performed in the above-mentioned studies, the incidence of ventricular arrhythmias may have been underestimated. A number of studies have described the incidence of ventricular arrhythmias in the setting of thrombolytic therapy using continuous Holter monitoring (Table 1.2). There are considerable differences in the incidence of early ventricular arrhythmias compared to studies from the prethrombolytic era. In an extensive review, Bigger et al. estimated the incidence of various forms of postinfarction ventricular arrhythmias before the introduction of thrombolytic therapy. In a total of 1443 patients, 10% had AIVR in the in-hospital period (range of 8% to 46% in various studies), compared to 60% (range 7% - 90%) in 733 patients with thrombolytic therapy (Table 1.2). Similarly, Bigger et al. described a VT incidence of 18.5% in 3698 patients (range 6% - 40%), monitored continuously during their stay in the CCU, compared to a 60% VT incidence (range 6% - 90%) in the 733 patients who underwent thrombolytic therapy. Two other studies have investigated the incidence of ventricular arrhythmias after thrombolytic therapy in a placebo-controlled design using 24-hour Holter monitoring. Wilcox et al. found a significant increase in the incidence of ventricular premature beats, pairs, and VT in patients treated with alteplase within 5 hours after symptom onset. Alexopoulos et al. found no difference in the incidence of ventricular arrhythmias after streptokinase or placebo during 24-hour Holter monitoring. However, when patients with a duration of symptoms less than or equal to 6 hours were considered separately, a higher incidence was seen in patients treated with streptokinase. Therefore, the higher incidence of ventricular arrhythmias (except VF) after thrombolytic therapy is more apparent when this treatment is applied early after the onset of symptoms.

In some of the studies investigating the incidence of ventricular arrhythmias after myocardial infarction, the relevance of a patent infarct-related artery after thrombolysis has been addressed. Zehender et al. found nonsustained VT in 95% of 22 patients with successful thrombolysis compared to 38% of eight patients with no reperfusion (p < 0.01). In addition, AIVR was also more frequent in those with a patent infarct-related artery 120 minutes after thrombolytic therapy (82% vs 63%). The observation that AIVR may be related to successful reperfusion had been described previously. Heidbüchel et al. found no difference in the incidence of nonsustained VT (77% vs 79%) or AIVR (74% vs 69%) in patients with or without successful reperfusion. However, since angiog-
raphy was not performed until 10-14 days after myocardial infarction, reocclusion during this interval may have disturbed the relation between reperfusion and ventricular arrhythmias. Similar to the study by Zehender et al., all patients with VF that had angiography (3/6) showed an occluded infarct-related artery. Data from the Thrombolysis In Myocardial Infarction (TIMI) Phase II database on 2546 patients have confirmed that sustained VT and VF after thrombolytic therapy are more frequent in patients with an occluded infarct-related artery.

In conclusion, the initial concern that thrombolytic therapy would produce life-threatening ventricular arrhythmias upon reperfusion has not become reality. Although the effect of thrombolysis on VF very early after the onset of symptoms (e.g., within 1 hour) is still controversial, thrombolytic therapy administered within 6 hours does not increase the incidence of VF up to 24 hours. Moreover, thrombolysis appears to actually reduce the incidence of VF during the remaining in-hospital period. Studies using coronary angiography have suggested that early VF and sustained VT are related to an occluded infarct-related artery, and thus unsuccessful reperfusion. Conversely, nonsustained VT and AIVR do occur more frequently after thrombolytic therapy, especially within 6 hours after onset of treatment. It has been suggested that these arrhythmias, and particularly AIVR, are predictors of successful thrombolysis. However, these signs of reperfusion are not very sensitive.

Time course of early ventricular arrhythmias

In a natural history study, Campbell et al. described the incidence and time course of ventricular arrhythmias in the first 12 hours after myocardial infarction. Three hours after the onset of myocardial infarction, the incidence of VF dropped, while other arrhythmias, including ventricular premature beats and VT, increased in incidence. These data are in agreement with another prethrombolytic study by Northover et al., who found the prevalence of VT to increase up to 12 hours after the onset of symptoms. A similar distribution of ventricular arrhythmias was observed in one of the major thrombolyis trials, the Anglo-Scandinavian Study of Early Thrombolysis (ASSET). Compared to placebo, paired ventricular premature beats and VT during Holter monitoring were more frequent in the 12-hour period after infarction in patients treated with alteplase. After this period, the incidence dropped gradually in both alteplase- and placebo-treated patients, and a difference between these two groups could no longer be discerned.
2.2. Late ventricular arrhythmias after thrombolytic therapy

The incidence of ventricular arrhythmias rapidly declines after the acute phase of myocardial infarction (Figure 1.1). As opposed to early ventricular arrhythmias, in which myocardial ischemia and reperfusion are major etiologic factors, infarct size, remodeling of the ventricle, and neurohumoral activation become more important in the cause of late ventricular arrhythmias. Since thrombolytic therapy has a beneficial influence on these factors, a reduction of late ventricular arrhythmias may be expected.

Late ventricular tachycardia

Figure 1.1. The incidence of various forms of ventricular arrhythmias during Holter monitoring in CATS is depicted. A rapid decrease in the percentage of patients with ventricular arrhythmias is observed after the early phase of myocardial infarction. VPBs indicates ventricular premature beats; AIVR, accelerated idioventricular rhythm; VT, ventricular tachycardia.
Most studies describing late ventricular arrhythmias have assessed their incidence in the period shortly before hospital discharge, with special interest in risk assessment of future arrhythmic events. In a review from the 1970s, VT was reported in 3% - 14% of myocardial infarction patients before hospital discharge.\textsuperscript{15} In patients participating in the Multi-Center Post Infarction Program,\textsuperscript{62} VT was reported in 11% of all patients. In this prethrombolytic study, predischarge VT during Holter monitoring was a strong independent predictor of arrhythmic events during patient follow up. In a large study where all patients received thrombolytic therapy, the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto myocardico (GISSI-2) trial,\textsuperscript{63} the incidence of nonsustained VT before discharge was 7%. A direct comparison of VT in patients who did or did not receive thrombolytic therapy during the late in-hospital period was performed by Turitto et al.\textsuperscript{64} These investigators found nonsustained VT in 13% of patients with thrombolytic therapy and in 11% of patients without thrombolytic therapy during 24-hour Holter monitoring (difference not significant). Only one patient, not treated with thrombolysis, experienced sustained VT. In conclusion, a considerable variance in the incidence of predischarge VT is observed, both with and without thrombolytic therapy, and no unambiguous treatment effect can be discerned. In addition, it has been suggested that VT in this period is primarily related to left ventricular dysfunction and relatively independent of the presence or absence of reperfusion.\textsuperscript{65}

Studies that describe the incidence of VT after hospital discharge are scarce. In a review by Willems,\textsuperscript{66} the incidence of late VT varies between 1% and 19%. The recorded incidence proves strongly dependent on the duration of Holter monitoring; a recording time of less than 24 hours rapidly reduces the number of episodes of VT recorded. Furthermore, when the incidence is estimated only on the basis of a patient history, especially nonsustained VT may not add to the incidence rate since it can easily occur without symptoms.

Programmed electrical stimulation may be helpful to identify patients at risk of late VT. Kersschot et al.\textsuperscript{57} investigated the induction of ventricular arrhythmias in patients randomly assigned to streptokinase therapy or conservative treatment. Induction of sustained monomorphic VT 26 days after myocardial infarction occurred more frequently in patients treated conservatively, affecting all 15 control patients (100%). By contrast, just 10 of 21 patients (48%) treated with streptokinase were inducible after a maximum of 3 extra stimuli (p < 0.001). Seventeen patients in the streptokinase group (81%) showed early reperfusion versus no patients in the control group. Bourke et al.\textsuperscript{68} also described a significant reduction in the number of patients that were electrically inducible after thrombolytic therapy. Similar to the study by Kersschot et al.,\textsuperscript{57} this finding
did not reveal a lower incidence of ventricular arrhythmias during follow-up care.

Sudden cardiac death

In prethrombolytic studies, an incidence of sudden death of around 10% has been reported in the first 6 months after myocardial infarction.\textsuperscript{15} Most major thrombolysis trials have provided information only about the overall cardiac mortality late after myocardial infarction. However, in the APSAC Intervention Mortality Study (AIMS)\textsuperscript{37} sudden cardiac death was reported separately: 25 patients (4.0%) died suddenly in the treated group versus 40 patients (6.3%) in the placebo group up to one year after myocardial infarction (RR 0.64, 95% CI: 0.39-1.03). In the GISSI-2 study,\textsuperscript{69} in which all patients received thrombolytic therapy, 84 of 8676 patients (1%) died suddenly in the first 6 months after myocardial infarction. Therefore, there are indications that not only total mortality but also sudden cardiac death may be reduced after thrombolytic therapy.

In conclusion, the application of thrombolytic therapy has beneficially altered the natural history of myocardial infarction with respect to the occurrence of life-threatening ventricular arrhythmias. However, ventricular arrhythmias still are an important cause of death after myocardial infarction and it remains of great importance to assess the clinical profile of the patient at risk for arrhythmic events. In the following paragraphs attention will be focused on two important risk factors: left ventricular dilatation and neurohumoral activation.

§ 3. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction: importance of left ventricular dilatation

In the last decade, many research efforts have been directed at the understanding of left ventricular remodeling after acute myocardial infarction. Left ventricular remodeling is defined as changes in the topography of both the infarcted and noninfarcted regions of the ventricle.\textsuperscript{70} It has become clear that this process has important prognostic implications\textsuperscript{10} given the fact that there are now studies available that demonstrate the beneficial effect of modulation of this process.\textsuperscript{71} In most studies, emphasis is placed on the functional and anatomical changes that result in remodeling of the left ventricle. These include infarct expansion, left ventricular hypertrophy, and left ventricular dilatation. However, there is increasing experimental evidence available that these anatomical
changes are paralleled by changes in electrophysiologic properties. Among these are increased dispersion in refractoriness, delayed conduction, and the appearance of afterdepolarizations which may explain the high incidence of ventricular arrhythmias in patients with progressive remodeling of the left ventricle.

3.1. Left ventricular remodeling after myocardial infarction

The process of left ventricular remodeling begins immediately after the onset of acute myocardial infarction. Within seconds of a coronary artery occlusion, wall motion abnormalities occur and an overall increase in left ventricular dimensions can be observed. This early form of left ventricular dilatation compensates functionally for the locally damaged myocardium and usually results in a normalized stroke volume (“functional dilatation”). During the following days a local inflammatory reaction and edema is observed in the infarcted area. Subsequently, over a period of weeks to months, proliferation of fibroblasts occurs and the number of collagen fibers increases. This is paralleled by resorption of necrotic material, and thus scar tissue is generated. Before completion of scar formation, the infarcted area is very vulnerable to straining forces. Dilatation and thinning of this area can easily occur due to slippage of myocytes. This part of the remodeling process is usually referred to as infarct expansion. Infarct expansion occurs on top of early functional dilatation and is the main determinant of left ventricular dilatation in the first few days after myocardial infarction. After this period, dilatation of the noninfarcted area gradually becomes more important. Dilatation of the noninfarcted area appears to be primarily dependent on the size of the infarcted area and preceding infarct expansion. Early left ventricular dilatation, thinning of the infarcted ventricular wall, and increased filling pressures all contribute to an increase in wall stress, which in turn may further promote left ventricular dilatation (“dilatation begets dilatation”) even when scar formation is completed. Pfeffer et al. demonstrated an additional 30% increase in end-diastolic volume 3 months after completion of scar tissue formation in rats. Besides dilatation of infarcted and noninfarcted areas, left ventricular hypertrophy is an integral part of the remodeling process. This can be considered a compensatory mechanism for the loss of functional myocardium. According to La Place’s law, an increase in wall thickness would result in a reduction of wall tension and subsequently prevent further dilatation. However, in experimental studies it has been observed that if 40% or more of the left ventricle is infarcted, hypertrophy as a compensatory mechanism fails and progressive dilatation will occur. A critical infarct size above which dilatation can not be compensated for has not been established in patients.
3.2. Association of left ventricular remodeling with arrhythmogenesis

Patients with progressive remodeling of the left ventricle, especially those with symptoms of heart failure, are characterized by a high incidence of ventricular arrhythmias. Sudden death rates from 4% to 86% have been reported, with most studies citing an incidence of around 50%. An association between the process of left ventricular remodeling and the occurrence of ventricular arrhythmias can therefore be assumed.

Early phases of remodeling: scar tissue formation and infarct expansion

Early after the onset of the remodeling process, relations between anatomical changes and arrhythmogenesis emerge (Table 1.3). An anatomical substrate for ventricular arrhythmias may be created even before completion of scar tissue formation. This anatomical substrate usually arises at the rim of the infarcted area and consists of islands of viable and nonviable myocardium, creating regional differences in conduction velocity and refractory period. De Bakker et al. recently demonstrated that slow conduction in these areas is not caused by a reduced conduction velocity, but by a ‘zig-zag’ course of activation. In 50% of all postinfarction patients without spontaneously occurring sustained ventricular arrhythmias, a sustained VT may be inducible 3 weeks after the onset of myocardial infarction. However, sustained ventricular arrhythmias only occur in a minority of patients. Apparently, next to an anatomical substrate and adequate triggering (e.g., by a ventricular extrasystole), additional factors that produce changes in activation and/or repolarization characteristics such as myocardial ischemia, increase in wall stress, electrolyte imbalance, or neurohumoral activation are needed to produce a sustained ventricular arrhythmia.

Another factor that may promote reentry is distension of the infarcted area, or so-called infarct expansion. When infarct expansion is progressive, aneurysm formation can occur in the early phase of left ventricular remodeling. In patients with early left ventricular aneurysm formation, mortality is high with a high percentage of sudden deaths. Meizlish et al. reported a mortality rate of 61% in 18 patients in the first year after myocardial infarction with 55% of these deaths classified as sudden. Because of its relation to early infarct expansion, these authors referred to the early appearance of a left ventricular aneurysm as ‘expanseurysm’. Not all ventricular aneurysms lead to life-threatening ventricular arrhythmias. The presence or absence of late potentials, a marker of a possible
substrate for reentry, is a powerful predictor of these arrhythmias during follow-
up care.\textsuperscript{87,88} Increased wall stress at the border of the aneurysm is another factor
that may promote arrhythmogenesis.\textsuperscript{89}
In addition, there are indications that beta-receptors are up-regulated in the
transition zone between aneurysm and normal myocardium.\textsuperscript{90} This may cause
local differences in effects of circulating catecholamines, resulting in an in-
creased dispersion in refractoriness.\textsuperscript{91} After thrombolytic therapy, propensity
towards development of ventricular arrhythmias in patients with a left ven-tri-
cular aneurysm is clearly reduced. Sager et al.\textsuperscript{92} studied 32 patients with a left
ventricular aneurysm half of which received thrombolytic therapy. Thirteen
days after myocardial infarction, VT could be induced in 88% of those without
thrombolytic therapy versus only 8% of those in the thrombolysis group. In
addition, 50% of the patients who did not receive thrombolytic therapy died
suddenly or had a sustained VT, whereas no arrhythmic events occurred in the
thrombolysis group. Thus, it appears that electrophysiologic stability is in-
creased after thrombolytic therapy in patients with left ventricular aneurysm.

Later phases of remodeling: left ventricular hypertrophy

Little is known about the role of compensatory hypertrophy in the genesis of
ventricular arrhythmias after myocardial infarction. Most information on the re-

<table>
<thead>
<tr>
<th>Phase of remodeling</th>
<th>Arrhythmogenic factor</th>
<th>Possible mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scar tissue formation</td>
<td>anatomical substrate</td>
<td>reentry in presence of modulating factors</td>
</tr>
<tr>
<td>Infarct expansion (aneurysm formation)</td>
<td>local stretch, beta-receptors ↑</td>
<td>SIAs, EADs, DADs, dispersion ↑</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>fibrosis, coronary reserve ↓, calcium overload</td>
<td>slow conduction↓, ischemia↑, DADs</td>
</tr>
<tr>
<td>LV dilatation</td>
<td>stretch, slippage, uncoupling, sympathetic dysfunction</td>
<td>SIAs, EADs, DADs, slow conduction↑, dispersion ↑</td>
</tr>
</tbody>
</table>

DADs indicates delayed afterdepolarizations; EADs, early afterdepolarizations; SIAs, stretch-induced afterdepolarizations; LV, left ventricular. \textsuperscript{#} factors promoting reentry.
ation between ventricular hypertrophy and ventricular arrhythmias has been obtained from human patients or animals with hypertension.\textsuperscript{93-96} From these studies it is clear that left ventricular hypertrophy is a potent arrhythmogenic factor. Data from the Framingham study indicate that patients with ventricular hypertrophy have a five-fold increase in risk of sudden cardiac death.\textsuperscript{94} The underlying mechanisms of the increased incidence of ventricular arrhythmias in the setting of ventricular hypertrophy is probably multifactorial. Myocardial ischemia induced by a limited coronary reserve, reentry promoted by interstitial fibrosis, and increased sympathetic activity all add to an accelerated process of arrhythmogenesis.\textsuperscript{95} In patients with left ventricular hypertrophy and inducible ventricular arrhythmias the incidence of late potentials is high, suggesting an important role of delayed conduction as a mechanism for these arrhythmias.\textsuperscript{96} On a molecular level, it has been shown that the buffering capability of intracellular calcium is reduced in hypertrophied myocytes. Therefore calcium homeostasis is fragile, and an increased calcium load could generate oscillatory electrical currents (such as DADs) which may lead to ventricular arrhythmias to occur.\textsuperscript{97,98} In the case of myocardial infarction, left ventricular hypertrophy often coexists with left ventricular dilatation and myocardial ischemia. These three factors all interact and augment each other in causing ventricular arrhythmias.\textsuperscript{99} Since left ventricular hypertrophy and dilatation occur simultaneously as part of the remodeling process, it may be difficult to assess their individual contributions.

Although the role of ventricular hypertrophy in the occurrence of ventricular arrhythmias after myocardial infarction is not yet fully established, it may be of major importance considering its arrhythmogenic potential in patients with hypertension.

**Left ventricular dilatation**

The residual left ventricular function after myocardial infarction is largely determined by the degree of left ventricular dilatation. Traditionally, left ventricular function has been expressed as the ejection fraction. Results from the Multicenter Postinfarction study\textsuperscript{100} show that ejection fraction is a powerful predictor of mortality during the first two years after myocardial infarction. In addition, its predictive value for the occurrence of ventricular arrhythmias is also well established.\textsuperscript{101} However, ejection fraction may not be a very sensitive measure of left ventricular dilatation. Considerable dilatation of the left ventricle can occur while the ejection fraction remains relatively unchanged. White et al.\textsuperscript{10} compared the prognostic value of ejection fraction and end-systolic volume assessed by angiography in 605 patients 4-8 weeks after acute myocardial i-
farction. They found that end-systolic volume was a more powerful predictor of death after myocardial infarction than ejection fraction. In addition, this variable was the most powerful independent predictor of deaths that occurred suddenly, suggesting an important role for left ventricular dilatation in the genesis of life-threatening ventricular arrhythmias. After the introduction of thrombolytic therapy, ejection fraction has still remained an important determinant of arrhythmic events. It has been suggested that its predictive value is independent of the result of thrombolytic therapy. The prognostic importance of left ventricular dilatation in this setting is less well known.

3.3. Mechanisms of arrhythmogenesis in left ventricular dilatation

Although the importance of left ventricular dilatation for the occurrence of ventricular arrhythmias has been well recognized, knowledge of the underlying mechanisms of these arrhythmias is incomplete. However, it is clear that the arrhythmogenic effect of dilatation is multifactorial in origin, and includes mechanical, electrical, and neurohumoral components. There are indications that specialized stretch-activated membrane channels can induce a depolarizing current during diastole, leading to stretch-induced afterdepolarizations (SIAs) which may trigger one or more ectopic beats. Recently, the existence of stretch-induced arrhythmias was demonstrated in the isolated canine left ventricle. In this study by Hansen et al., a sudden increase in diastolic volume (induced by an intracavitary balloon) induced frequent premature ventricular contractions, occasional ventricular couplets, and nonsustained VT. In the isolated Langendorff-perfused rabbit heart, Franz et al. showed that both gradual and sudden increases of left ventricular volume induced a reduction of the membrane potential. However, premature ventricular contractions were especially seen in the case of a sudden volume increase.

Next to SIAs and subsequent ventricular arrhythmias, effects on duration of repolarization have been described in terms of an increase in volume. Reiter et al. described the electrophysiological effects of acute ventricular dilatation in the isolated rabbit heart. They found that an increase in left ventricular volume did not affect pacing threshold or conduction velocity, but instead reduced the effective refractory period in a heterogeneous manner thereby increasing the temporal dispersion in recovery. In the infarcted ventricle, Calkins et al. noted a more pronounced reduction of the refractory period in infarcted compared to noninfarcted sites of the ventricle when volume load was applied. This increase in refractoriness was paralleled by a conversion from noninducible to inducible VT in 4 of 8 ventricles when volume loading was applied. In humans, effects of volume and/or pressure loading on repolarization charac-
teristics have been demonstrated during balloon angioplasty,\textsuperscript{107} performance of the Vasalva maneuver,\textsuperscript{108} and after weaning from extracorporeal life support.\textsuperscript{109} In these studies, acute changes of left ventricular loading were accompanied by a reduction of the refractory period and increased dispersion in refractoriness.\textsuperscript{109} In addition, the appearance of EADs capable of inducing triggered activity was noted.\textsuperscript{107,108} In these human studies DADs were not observed. However in animal studies, an increase in the amplitude of DADs has been observed when applying stretch to myocardial tissue.\textsuperscript{110}

Most of the above-mentioned studies have described electrophysiological changes in reaction to sudden changes in volume or pressure load in noninfarcted ventricles. Whether these changes persist after a longer period of increased loading and also apply in the setting of acute myocardial infarction remains unknown. In the latter case, slowly progressive left ventricular dilatation, characterized by cell slippage, may lead to cellular uncoupling,\textsuperscript{111} which in turn may induce slow conduction and increased dispersion in refractoriness, possibly adding to the development of late ventricular arrhythmias.

3.4. Effect of thrombolytic therapy on left ventricular dilatation and related ventricular arrhythmias

Thrombolytic therapy interferes in the relation between remodeling and ventricular arrhythmias on several levels. Infarct size is reduced after successful thrombolysis,\textsuperscript{58} thus reducing the probability of an anatomical substrate for ventricular arrhythmias to be formed. In addition, experimental studies have shown that reperfusion several hours after coronary occlusion reduces infarct expansion independent of infarct size.\textsuperscript{112,113} Accelerated healing of the infarcted area has been proposed as the most likely underlying mechanism.\textsuperscript{112} This process may explain the reduced incidence of ventricular aneurysm after thrombolytic therapy.\textsuperscript{85} In addition, less compensatory hypertrophy will occur, and areas of the ventricle showing delayed conduction will be limited. Together with a reduction of infarct size, this finding may explain the lower incidence of late potentials in patients with successful reperfusion.\textsuperscript{114-117} Furthermore, left ventricular dilatation is reduced when thrombolytic therapy results in a patent infarct-related artery.\textsuperscript{60,118}

In summary, the process of left ventricular remodeling has several aspects which may promote the occurrence of ventricular arrhythmias after myocardial infarction. Left ventricular dilatation is of particular interest because this aspect of remodeling is clearly related to the occurrence of life-threatening postinfarction ventricular arrhythmias. The underlying electrophysiological mechanisms
of this relation are not fully elucidated, but may include delayed conduction and dispersion in refractoriness. The reduced incidence of ventricular arrhythmias after thrombolytic therapy may be explained, at least in part, by its modulating effects on left ventricular remodeling.

§ 4. Neurohumoral activation as an etiologic factor for early and late ventricular arrhythmias

Neurohumoral activation after myocardial infarction includes increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone (RAA) system. Under normal circumstances, these systems are balanced by
parasympathetic activity and atrial natriuretic peptide. In the setting of acute myocardial infarction this balance is lost and a relative increase of sympathetic tone and activation of the RAA system is observed both of which may have arrhythmogenic effects. Increased sympathetic activity is usually seen up to 24-48 hours after infarction, whereas activation of the (systemic) RAA system is not observed until after this period (Figure 1.2).

4.1. Sympathetic nervous system activity and ventricular arrhythmias after acute myocardial infarction

The role of increased sympathetic activity in the cause of ventricular arrhythmias is well established. An increase in sympathetic tone can promote ventricular arrhythmias by inducing hypokalemia, increasing heart rate, and by enlarging ischemic areas. Electrophysiological effects include an increase in firing rate in the case of abnormal automaticity, and the induction of triggered activity by augmenting EADs and DADs. It is generally accepted that the electrophysiological effects of beta-adrenergic stimulation are predominantly mediated through cyclic adenosine monophosphate (cAMP). These effects include augmentation of the plateau phase and an increase in the rate of repolarization resulting in a shorter action potential duration. Reentry can occur due to the heterogeneous distribution of sympathetic nerve fibers. Under normal circumstances an increase in sympathetic tone does not lead to changes in the distribution of refractory periods. However, in diseased (e.g., infarcted) ventricles regional dysfunction of sympathetic nerves can lead to increased dispersion in refractoriness. Calkins et al. recently reported on 11 patients with life-threatening ventricular arrhythmias referred for placement of an implantable defibrillator. The pattern of sympathetic innervation was assessed using scintigraphy with $^{11}$C-hydroxyephedrine; regional refractory periods were measured intraoperatively. The investigators showed a clear correlation between regional sympathetic dysfunction and ventricular refractoriness. This may suggest that differences in refractory period could increase in the case of sympathetic stimulation, leading to a higher probability of successful reentry as a mechanism for ventricular arrhythmias.

Increased sympathetic activity early after myocardial infarction

In experimental models it has been shown that norepinephrine levels are elevated within one minute of coronary artery occlusion. The role of norepinephrine in the incidence of ventricular arrhythmias is supported by studies that demonstrate a lower threshold for VF upon direct stimulation of sympathetic
nerves in the setting of myocardial ischemia. In addition, complete abolition of ventricular arrhythmias has been shown after denervation of the heart before ligation of a coronary artery. In humans, activation of the sympathetic nervous system has also been observed early after the onset of myocardial infarction. The extent and duration to which sympathetic activity is increased has been found to relate to infarct size and degree of left ventricular dysfunction. In a study by Benedict et al., epinephrine and norepinephrine levels returned to normal by the third day in patients with uncomplicated myocardial infarction. However, in patients with cardiogenic shock these levels did not normalize. Sigurdsson et al. observed in 55 patients participating in the second COoperative North Scandinavian ENalapril SURvival Study (CONSENSUS II) that catecholamines returned to normal within a few days in patients with uncomplicated myocardial infarction, but remained elevated in patients with signs of congestive heart failure. In the Survival And Ventricular Enlargement (SAVE) study, which investigated patients with left ventricular dysfunction but no overt heart failure after myocardial infarction, a wide variety of sympathetic activity was found. Some patients with a low ejection fraction who required use of diuretics showed no neurohumoral activation, whereas other patients with a relatively preserved ejection fraction and no use of diuretics did. Still, ejection fraction proved an independent predictor of norepinephrine and epinephrine levels before hospital discharge despite these exceptions. Elevated catecholamines shortly after myocardial infarction appear to have prognostic value for cardiac events during follow up. In 12 patients with acute myocardial infarction, Karlsberg et al. found that all patients with peak epinephrine values > 1000 pg/ml died during 18 months of follow up, while survivors had values < 1000 pg/ml. In addition, Sigurdsson et al. found significantly higher norepinephrine levels in the 6 out of 55 patients (11%) who died compared to survivors during 6 months of follow-up care (909 pg/ml vs 545 pg/ml). The authors attributed the difference in norepinephrine mainly to a difference in the extent of myocardial damage.

Heart rate variability early after myocardial infarction

Heart rate or heart period variability represents a measure of the degree of modulation of autonomic tone, in particular of parasympathetic activity. Its components are expressed as variables from the time domain (e.g., standard deviation of all RR intervals recorded in 24 hours) or frequency domain (high-and low-frequency components, obtained by spectral analysis). Although the exact underlying connection to activity of the autonomic nervous system has not been elucidated, evidence is available that reduced heart rate...
variability represents sympathovagal imbalance and has a clear value in predicting mortality and arrhythmic events after myocardial infarction. Casolo et al. found a reduced heart rate variability, measured on the second or third day after myocardial infarction, in patients with a large enzymatic infarct size, reduced left ventricular function, and Killip heart failure class ratings higher than I (for Killip classification, see box on this page). In contrast, patients with non-Q-wave infarction and those treated with rtPA showed a significantly higher heart rate variability. In this study, six patients died within 20 days of whom four died suddenly. These patients showed a significantly lower heart rate variability compared to survivors. The contribution of reperfusion after thrombolytic therapy was not clear, although patients treated with rtPA demonstrated a higher heart rate variability.

In conclusion, increased sympathetic activity in the early stages after myocardial infarction is associated with an adverse prognosis during follow up, due to an increased incidence of arrhythmic events.

Increased sympathetic activity late after myocardial infarction

As stated previously, catecholamine levels return to normal after a few days in uncomplicated myocardial infarction. However, in patients with reduced left ventricular function and clinical signs of heart failure, sympathetic activity remains elevated. Sigurdsson et al. measured norepinephrine levels up to one month after myocardial infarction and found significantly higher levels in patients with congestive heart failure. The difference in norepinephrine levels, compared to patients without heart failure, was further augmented when head-

<table>
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<th>KILLIP CLASSIFICATION</th>
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<tr>
<td>I. Absence of third heart sound. Absence of rales over lung fields.</td>
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<tr>
<td>II. Rales over &lt; 50% of the lung fields or third heart sound present.</td>
</tr>
<tr>
<td>III. Rales over ≥ 50% of the lung fields. Frequently pulmonary edema.</td>
</tr>
<tr>
<td>IV. Shock.</td>
</tr>
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up tilt testing was applied. The authors attributed this effect to altered cardiovascular control mechanisms or hypovolemia due to diuretic therapy in these patients. The site of myocardial infarction also appears to affect the pattern of recovery of autonomic function. Flapan et al.\textsuperscript{144} assessed heart rate variability in 20 patients with anterior or inferior myocardial infarction. They found that heart rate variability was relatively preserved in patients with inferior myocardial infarction, whereas a reduction of heart rate variability up to 6 weeks after admission was observed in patients with anterior myocardial infarction. Other studies have confirmed this prolonged sympathovagal imbalance in patients with anterior myocardial infarction.\textsuperscript{145,146}

Most studies assessing autonomic function by use of heart rate variability do so before hospital discharge to risk-stratify patients for life-threatening arrhythmias during follow-up care. In a large study of more than 400 patients, Farrell et al.\textsuperscript{57} showed that a reduced heart rate variability before discharge had important value in predicting arrhythmic events independent of residual left ventricular function. These authors suggested that the latter may be explained by selective destruction of autonomic nerves without significant loss of left ventricular function in some patients. This situation could lead to sympathovagal imbalance with a reduced threshold for VF as a possible consequence.

Although persistent activation of the sympathetic nervous system is mostly encountered in patients with left ventricular dysfunction and/or signs of congestive heart failure, sympathovagal imbalance may also persist in some patients without cardiac failure. This may explain, at least in part, the occurrence of life-threatening ventricular arrhythmias in patients with relatively preserved left ventricular function.

4.2. Renin-angiotensin-aldosterone system activation and ventricular arrhythmias after acute myocardial infarction

Although the RAA system is not well known for its arrhythmogenic effects, there are some indications that an activated RAA system has electrophysiologic effects that may promote the occurrence of ventricular arrhythmias. De Langen et al.\textsuperscript{150} observed a shortening in sinus rhythm cycle length and refractory period upon infusion of angiotensin II in healthy pigs. In addition, the same investigators were able to induce sustained VT after angiotensin II infusion in 5 of 9 previously noninducible pigs 2 weeks after myocardial infarction. Fleetwood et al.\textsuperscript{151} demonstrated in the isolated rat heart that the duration of VF upon reperfusion was significantly reduced by a selective angiotensin II receptor antagonist. The authors suggested that VF was maintained by locally-produced angio-
tensin II which could explain the beneficial effects of ACE inhibitors on reperfusion VF.

Local renin-angiotensin system in cardiac tissue

There is now convincing evidence available for the existence of a local renin-angiotensin system in the heart\(^\text{152}\) which may explain the findings mentioned in the previous paragraph. Besides direct electrophysiological effects, locally-produced angiotensin II interferes with the release of norepinephrine from sympathetic nerve endings. Angiotensin II promotes presynaptic norepinephrine release, blocks presynaptic norepinephrine reuptake, increases catecholamine synthesis, and potentiates postsynaptic actions of norepinephrine.\(^\text{153}\) This activity may further enhance the propensity towards ventricular arrhythmias by mechanisms described in paragraph 4.1. In addition, angiotensin II has important vasoconstrictive properties which could expand the ischemic area in the case of acute myocardial infarction.\(^\text{20}\) Ertl et al.\(^\text{154}\) demonstrated that collateral flow was increased by ACE inhibition during coronary artery occlusion, resulting in a smaller infarct size in 21 anesthetized dogs. However, a bradykinin-mediated mechanism could not be excluded in this study. Angiotensin II also has properties as a local growth factor, and may be partly responsible for the compensatory left ventricular hypertrophy observed after myocardial infarction.\(^\text{155}\) Left ventricular hypertrophy, in turn, is a well-known risk factor for ventricular arrhythmias (paragraph 3.2). It has been shown recently that the propensity for ventricular hypertrophy may be mediated by genetic disposition. Schunkert et al.\(^\text{156}\) found a clearly-increased risk for left ventricular hypertrophy in normotensive patients who were homozygous for the deletion (D) allele of the ACE gene. This genotype is associated with high levels of ACE and is frequently present in patients with coronary artery disease.\(^\text{157}\) In addition, patients with this genotype are highly prone to left ventricular dilatation in the first year after myocardial infarction.\(^\text{158}\) This result may stem from the form of hypertrophy that results in lengthening of myocytes.\(^\text{159}\) Considering these factors, an increased incidence of ventricular arrhythmias may be anticipated in patients that are homozygous for the D allele of ACE.

4.3. Effect of thrombolytic therapy on neurohumoral activation

Effect on sympathetic activity

In animal studies, an increase in norepinephrine overflow is observed upon reperfusion of a previously ligated coronary artery.\(^\text{9}\) Depending on the duration
of preceding ischemia, this finding is paralleled by various types of reperfusion arrhythmias (see paragraph 1). In humans, data on norepinephrine levels early after thrombolytic therapy for acute myocardial infarction is limited. Sigurdsson et al. assessed norepinephrine levels within 24 hours after the onset of symptoms of acute myocardial infarction in 34 patients. There was no difference in norepinephrine levels between the 18 patients who were treated and the 16 patients who were not treated with intravenous streptokinase. However, patients not receiving thrombolytic therapy were included significantly later after the onset of symptoms, which may have disturbed the relation between reperfusion and norepinephrine levels. Moreover, angiographic data were not available in this study. Zabel et al. measured heart rate variability within the first hour of thrombolytic therapy. They found a significant increase in parasympathetic activity in patients with successful thrombolysis compared to those without successful thrombolytic therapy. Other studies describing the effect of thrombolytic therapy on heart rate variability late after myocardial infarction have shown similar results. In addition, Pedretti et al. showed that this effect on autonomic tone was paralleled by a decrease in inducible and spontaneously-occurring ventricular arrhythmias. This result implies that a considerable discrepancy exists between experimental and clinical findings. The release of norepinephrine upon reperfusion in animal experiments has been attributed to a number of factors that lead to depolarization of sympathetic nerve endings, including hyperkalemia, acidosis, hypoxia, and formation of membrane-active metabolites. This local release of norepinephrine may be small in comparison to the systemic release of neurohormones caused by hemodynamic stress during acute myocardial infarction. Therefore in the case of successful thrombolysis, the hemodynamic benefit of reperfusion may outweigh local overflow of norepinephrine, resulting in lower overall systemic levels of this neurohormone. It has been shown that thrombolysis prevents early left ventricular dilatation, a condition which would otherwise require an increase in sympathetic activity to maintain a sufficient stroke volume. This conclusion is supported by the findings of Zabel et al., who showed significantly lower heart rates in patients with a patent infarct-related artery during the first hour after thrombolytic therapy (70 ± 12 beats/minute vs 80 ± 13 beats/minute, P=0.003).

Effect on the RAA system

Data on the effects of thrombolytic therapy on the RAA system are limited. Thrombolytic therapy may prevent activation of the systemic RAA system by limiting infarct size and preventing early and late left ventricular dilatation. However, Nabel et al. still found elevated renin and angiotensin II levels up to...
7 days after thrombolytic therapy in 29 patients, 28 (97%) of whom had a patent infarct-related artery (successful PTCA for an occluded infarct-related artery was performed in eight patients). Thus, even when successful, reperfusion can not fully prevent activation of the RAA system after acute myocardial infarction.

In summary, both sympathovagal imbalance and activation of the RAA system may increase the propensity towards ventricular arrhythmias after acute myocardial infarction. A relative increase of sympathetic activity reduces the threshold for ventricular arrhythmias by inducing hypokalemia, increasing heart rate, and augmenting EADs and DADs. Sympathetic activity usually returns to normal after a few days, but remains increased in patients with reduced left ventricular function and/or signs of heart failure. However, locally-damaged autonomic nerve fibers may also result in more dispersion in refractoriness in patients with preserved left ventricular function, hereby increasing the risk of ventricular arrhythmias. Studies using heart rate variability have shown that thrombolytic therapy reduces sympathovagal imbalance both early and late after myocardial infarction, paralleled by a reduction of inducible and spontaneously occurring ventricular arrhythmias. RAA activation after myocardial infarction may also increase the incidence of ventricular arrhythmias, primarily through the effects of angiotensin II. This compound has been demonstrated to reduce the refractory period and increase heart rate. In addition, the well-known vasoconstrictive effect of angiotensin II may also increase oxygen demand and thus promote ischemia, a powerful arrhythmogenic factor. Finally, long lasting RAA activation leads to left ventricular hypertrophy, which in turn is associated with an increased risk of ventricular arrhythmias. Recent evidence suggests that genetic predisposition plays a role in the development of left ventricular hypertrophy. Thrombolytic therapy may reduce, but not fully prevent activation of the RAA system after myocardial infarction.

§ 5. Interrelation between neurohumoral activation and left ventricular remodeling

Within seconds after the occlusion of a coronary artery by use of a PTCA catheter, wall motion abnormalities can be observed, even before the appearance of electrocardiographic abnormalities or anginal complaints. In addition, increased plasma levels of norepinephrine can be detected within 1 minute of coronary artery occlusion. Thus it appears that both activation of the sympathetic nervous system and left ventricular dysfunction commence rapidly after
CHAPTER 1

the onset of coronary occlusion. After 20-30 minutes, ischemia becomes irreversible, and myocardial infarction is completed in approximately 3-6 hours.\textsuperscript{161} In patients with small infarcts without clinical signs of heart failure, sympathetic activity gradually returns to normal in the following few days.\textsuperscript{132} In contrast, activation of the RAA system remains present even in limited infarctions.\textsuperscript{160} In patients with large infarcts (e.g., in patients with congestive heart failure) the sympathetic nervous system remains activated alongside an activated RAA system,\textsuperscript{132} presumably to maintain cardiac output. However, both systems increase wall stress of the left ventricle by various mechanisms and may thus accelerate remodeling and left ventricular dilatation in particular resulting in a poor outcome.\textsuperscript{133,134} In intermediate-sized infarctions, sympathetic activity may initially normalize but increase later when left ventricular remodeling has led to a reduced left ventricular function. Alternatively, neurohumoral activation may persist and add to infarct expansion and subsequent left ventricular dilatation. The degree of neurohumoral activation during the first days to weeks may be crucial for the resulting degree of left ventricular dilatation since the infarcted area is particularly sensitive to straining forces during this period.

Interaction on the cellular level: consequences for cardiac electrophysiology

Beau and Saffitz\textsuperscript{162} recently reported on regional sympathetic activity in failing human hearts, obtained after cardiac transplantation. They showed that the uptake of labeled norepinephrine in dilated ventricles was five-fold lower in subendocardial regions compared to subepicardial regions. The investigators postulated that a reduced uptake of norepinephrine in subepicardial regions would result in local down-regulation of beta-adrenergic receptors, which could lead to increased dispersion in refractoriness. Indeed, (regionally but not transmurally) increased dispersion in refractoriness, quantified by increased QT dispersion, has been reported in patients with chronic heart failure.\textsuperscript{163} In this particular study, this finding did not translate in an increased incidence of ventricular arrhythmias. However, the heterogeneous distribution of sympathetic activity appears to be an attractive additional explanation for the high incidence of ventricular arrhythmias in patients with left ventricular dilatation.\textsuperscript{10}

§ 6. Rationale for the use of ACE inhibition during thrombolytic therapy

Although no direct anti-arrhythmic effects of ACE inhibitors have been described,\textsuperscript{164} an indirect reduction of ventricular arrhythmias may be anticipated when these compounds are used in the setting of acute myocardial infarction. In general, blunting of neurohumoral activation, limitation of myocardial damage,
INTRODUCTION

and subsequent remodeling of the left ventricle may well result in a reduction of ventricular arrhythmias after acute myocardial infarction.

6.1. Effect on early ventricular arrhythmias

Experimental evidence

The importance of neurohumoral activation for the occurrence of ventricular arrhythmias in the early phases of coronary occlusion and reperfusion has been recognized for many years. In 1859 Einbrodt demonstrated that vagal nerve stimulation could protect the canine ventricle against VF. In addition, later experiments showed that cardiac denervation can prevent the occurrence of VF upon reperfusion. More recently, Sheridan et al. found that the release of norepinephrine was mediated by locally-produced angiotensin II. These findings raised the interest in determining the role of the renin-angiotensin system in the genesis of reperfusion arrhythmias. In the early 1980s van Gilst et al. studied the effect of captopril on reperfusion arrhythmias in the isolated rat heart. They found a clear-cut reduction in the incidence and duration of VF which appeared to follow a dose-response relation. This change was paralleled by a significant reduction of myocardial injury, quantified by purine loss, and outflow of catecholamines. However, the authors suggested that this result flowed from an angiotensin II-independent mechanism, since angiotensin II was not retrieved from the coronary effluent. Another study by the same group demonstrated that the antiarrhythmic effects of captopril were completely abolished by indomethacin which suggested a possible prostaglandin-dependent mechanism. Prostacyclin PGI₂ is known to inhibit the release of norepinephrine which could explain these findings. In the same study, enalapril did not appear to affect the occurrence of ventricular arrhythmias. However, other investigators have shown the cardioprotective effects of enalapril and ramipril, both ACE inhibitors without a sulfhydryl moiety. Grover et al. compared seven ACE inhibitors with different affinities for the local RAA system and agents with and without a sulfhydryl moiety. These authors found that the cardioprotective effects of ACE inhibitors were related to the presence of a sulfhydryl moiety and not to the degree of local ACE inhibition. Potentially beneficial effects of a sulfhydryl moiety may include scavenging of free radicals during reperfusion and coronary dilatation.

Clinical evidence
In humans, the effects of ACE inhibition on early ventricular arrhythmias after myocardial infarction, with or without thrombolytic therapy, have been investigated in a limited number of studies. Ambrozioni et al. investigated the effect of zofenopril therapy started within 24 hours after the onset of symptoms in patients not eligible for thrombolytic therapy in the Survival of Myocardial Infarction Long-term survival Evaluation (SMILE) pilot study (Table 1.4). No effect on the incidence of ventricular arrhythmias was reported. Ray et al. studied the effects of captopril therapy administered 6-24 hours (mean of 15) after the onset of symptoms of acute myocardial infarction. None of these patients received thrombolytic therapy. There was no difference in the incidence of ventricular arrhythmias during hospitalization. In addition, no effect on levels of catecholamines was seen.

The investigators did observe a reduction of left ventricular dilatation during 13 months of follow-up care. In the pilot study of the fourth International Study of Infarct Survival (ISIS-4) Pilipis et al. investigated the effects of captopril and mononitrate started a mean of 13 hours after the onset of symptoms therapy on the incidence of ventricular arrhythmias. The number of ventricular premature beats and VT during 48-hour Holter monitoring was reduced in patients treated with captopril or mononitrate. However, only the effect of mononitrate on premature beats reached statistical significance. In this pilot study, 92 of the 100 study patients received thrombolytic therapy. Bussmann et al. studied the effect of captopril on infarct size and ventricular arrhythmias in a placebo-controlled study of 46 patients with acute myocardial infarction. Thrombolytic therapy was given in 23 out of 46 patients (50%). Captopril was administered intravenously 2-18 hours (mean of 10) after the onset of symptoms. In the treated group, there was a significant reduction in the number of ventricular

<table>
<thead>
<tr>
<th>Author</th>
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<th>N</th>
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<td>99</td>
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<tr>
<td>Bussman</td>
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<tr>
<td>Di Pasquale</td>
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<td>72</td>
<td>≤ 4</td>
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AIVR indicates accelerated idioventricular rhythm; FU, follow up; h, hours; i.v., intravenous;
premature beats in 48-hour Holter recordings. In addition, seven patients in the placebo group had VF in the acute phase, compared to none in the treated group. Di Pasquale et al.\textsuperscript{177} used a different study design. These investigators compared in a total of 72 patients the effect of captopril administered 15 minutes before thrombolytic therapy with captopril administration 3-4 days after urokinase infusion. A significant reduction in early ventricular arrhythmias, observed within 2 hours after the onset of thrombolytic therapy, and predischarge ventricular arrhythmias was seen in the early treatment group compared to the late treatment group. From these studies it appears that a greater effect from captopril therapy can be expected when it is started earlier. The findings of Di Pasquale et al.\textsuperscript{177} are especially interesting in this respect.

The only other study describing the effect of captopril on the occurrence of ventricular arrhythmias during thrombolysis was the CATS pilot study.\textsuperscript{178} In this study, a low dose of captopril administered either orally or intravenously was given during thrombolysis. The incidence of nonsustained VT during the first 4 hours after onset of therapy was reduced in the orally-treated group but not in the intravenously-treated group. In the orally-treated group, this effect was paralleled by a significant reduction in plasma norepinephrine levels. In contrast, norepinephrine levels appeared to increase in the intravenously-treated group. This finding may have been induced by a serious drop in blood pressure observed in the latter group. The investigators attributed this effect to an interaction of intravenous captopril with streptokinase which both are known to intervene with the bradykinin metabolism resulting in a bradykinin-induced hypotensive response. Significantly more hypotension was also observed in the CONSENSUS II study in which patients were treated with intravenous enalapril within 24 hours after myocardial infarction.\textsuperscript{179} The CONSENSUS II investigators suggested that this early hypotensive reaction was responsible for the excess mortality in the active-treatment group. Therefore, when ACE inhibition is applied soon after myocardial infarction with or without thrombolytic therapy, the oral route of administration is clearly preferable.
6.2. Effect on late ventricular arrhythmias

Cardiac electrophysiology - results of programmed stimulation

As stated earlier, ACE inhibitors do not have direct anti-arrhythmic properties. However, effects on cardiac electrophysiology have been described. Kingma et al.\textsuperscript{180} investigated the effects of ACE inhibition on the inducibility of ventricular arrhythmias in pigs. Induction of VT was prevented in all six previously inducible pigs one week after myocardial infarction. There was a trend towards a reduction of the refractory period (253 ms vs 228 ms, not significant). The authors attributed the anti-arrhythmic effects of captopril to an indirect blocking effect on norepinephrine release mediated by angiotensin II. In another study by the same group,\textsuperscript{150} angiotensin II was infused in five healthy pigs. In contrast to the previous study, a significant decrease in refractory period (253 ms vs 228 ms, not significant) was observed. Furthermore, angiotensin II was administered in 17 pigs with myocardial infarction produced by coronary artery occlusion using a balloon catheter. Of nine previously noninducible animals, VT was inducible in five animals after infusion of angiotensin II and an additional increase in spontaneously occurring ventricular arrhythmias was observed. Of eight inducible pigs, five animals were no longer inducible after captopril infusion. The authors attributed this effect of captopril to the prevention of the deleterious effects of angiotensin II which had caused a reduction of refactororiness in parallel to an increase in heart rate and blood pressure.

Another pathway by which ACE inhibitors may reduce ventricular arrhythmias is via an increase in bradykinin levels. Since ACE is identical to kininase
II, the enzyme responsible for bradykinin breakdown,\textsuperscript{181} ACE inhibition will also lead to an increase in bradykinin levels. In six pigs with inducible sustained VT after myocardial infarction, Tobé et al.\textsuperscript{182} infused bradykinin to study its electrophysiological effects. No effect on the refractory period was seen. However, after bradykinin infusion, 4 of 6 pigs were no longer inducible. The authors suggested that a significant drop in blood pressure may have reduced wall stress which in turn could have prevented inducibility. This electrophysiological effect of a reduction in wall stress has been previously described.\textsuperscript{106}

Only one small study has investigated the electrophysiological effects of ACE inhibition in humans. In eight patients with previous myocardial infarction and inducible VT, Bashir et al.\textsuperscript{183} serially studied the electrophysiological effects of captopril and the combination of hydralazine and isosorbide dinitrate. The mean ejection fraction of these patients was 24\%. A significant increase in refractory period was measured after captopril therapy but not after hydralazine-nitrate therapy. However, no effect on inducibility was found. The difference between captopril and hydralazine-nitrate therapy was explained by a difference in sympathetic activity. After hydralazine-nitrate administration, an increase in heart rate from 68 beats/minute to 81 beats/minute was seen, whereas heart rate after captopril therapy was unchanged. The beneficial effect of unloading of the heart was probably counteracted by increased sympathetic activity during hydralazine-nitrate treatment, whereas this increase was blocked during captopril treatment.

Modifying the anatomical substrate - modulation of the remodeling process

Besides effects on cardiac electrophysiology caused by acute or subacute changes in loading conditions and modulation of sympathetic activity, other effects of ACE inhibitors may result in a reduction of late ventricular arrhythmias. For instance, a reduction in infarct size may reduce the probability of an anatomical substrate for ventricular arrhythmias to be formed, thus reducing the likelihood of the occurrence of late ventricular arrhythmias.\textsuperscript{82} There are several studies indicating that ACE inhibitors can reduce infarct size. Ertl et al.\textsuperscript{154} provided evidence that this result could be explained by a beneficial effect on coronary flow. In addition, Martorana et al.\textsuperscript{184} showed that the reduction in infarct size can be abolished by a bradykinin antagonist. Tobé et al.\textsuperscript{185} further demonstrated the importance of bradykinin in limiting infarct size. Infusion of bradykinin in pigs with a myocardial infarction produced by a balloon catheter in the left coronary artery resulted in significantly lower creatine kinase levels and a reduction in late potentials after 2 weeks (compared to a saline-treated
In addition, this finding was associated with a trend towards a reduction in inducible sustained VT. After thrombolytic therapy, ACE inhibitors containing sulfhydryl groups may theoretically have additional benefit by scavenging free radicals which may lead to less reperfusion damage. However, the contribution of reperfusion injury to total infarct size is still being questioned.

As discussed in paragraph 3.2, left ventricular remodeling after myocardial infarction can represent an important factor in the cause of ventricular arrhythmias. At present, numerous experimental and clinical studies with or without previous thrombolytic therapy have shown the modulating effect of ACE inhibitors on left ventricular dilatation. To date, data on the effects of ACE inhibition applied during thrombolytic therapy on left ventricular dilatation is limited. In addition, experimental studies have shown that early captopril treatment can prevent left ventricular hypertrophy after myocardial infarction. Finally, there are indications that a reduction in left ventricular hypertrophy by ACE inhibition can contribute to a reduction of life-threatening ventricular arrhythmias.

Neurohumoral activation and electrolytes

From studies investigating patients with heart failure it has become clear that norepinephrine levels are reduced during chronic treatment with ACE inhibitors. In addition, recent studies have demonstrated that ACE inhibition can
Table 1.5. Effect of ACE inhibitors on late ventricular arrhythmias in patients with heart failure

<table>
<thead>
<tr>
<th>Author</th>
<th>Compound</th>
<th>N</th>
<th>Selection</th>
<th>Protocol</th>
<th>Follow up</th>
<th>Effect on VAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleland 1984*</td>
<td>captopril</td>
<td>14</td>
<td>NYHA 3-4</td>
<td>double-blind, crossover</td>
<td>2 months</td>
<td>VPBs, pairs, VT ↓</td>
</tr>
<tr>
<td>Cleland 1985*</td>
<td>enalapril</td>
<td>20</td>
<td>NYHA 2-4</td>
<td>double-blind, crossover</td>
<td>1.5 months</td>
<td>VPBs ↓</td>
</tr>
<tr>
<td>Webster*</td>
<td>enalapril</td>
<td>19</td>
<td>NYHA 2-3</td>
<td>double-blind</td>
<td>3 months</td>
<td>VPBs, pairs, VT ↓</td>
</tr>
<tr>
<td>Captopril-Digoxin*</td>
<td>captopril</td>
<td>300</td>
<td>NYHA 2</td>
<td>double-blind</td>
<td>6 months</td>
<td>VAs ↓ vs digoxin</td>
</tr>
<tr>
<td>De Graeff*</td>
<td>captopril</td>
<td>12</td>
<td>NYHA 3-4</td>
<td>open design</td>
<td>3 months</td>
<td>no effect on VAs</td>
</tr>
<tr>
<td>Cocchieri*</td>
<td>captopril</td>
<td>22</td>
<td>NYHA 1-2</td>
<td>double-blind</td>
<td>3 months</td>
<td>no effect on VAs</td>
</tr>
<tr>
<td>Bechler-Lisinska*</td>
<td>captopril</td>
<td>50</td>
<td>NYHA 3-4</td>
<td>open design</td>
<td>1 month</td>
<td>VPBs, VT ↓</td>
</tr>
<tr>
<td>Kleber*</td>
<td>captopril</td>
<td>93</td>
<td>NYHA 1-3</td>
<td>double-blind</td>
<td>32 months</td>
<td>no effect on VPBs</td>
</tr>
<tr>
<td>Pomini*</td>
<td>enalapril</td>
<td>30</td>
<td>NYHA 3-4</td>
<td>open</td>
<td>2 months</td>
<td>VPBs, pairs, VT ↓</td>
</tr>
<tr>
<td>Poquet*</td>
<td>captopril</td>
<td>47</td>
<td>NYHA 2-3</td>
<td>open</td>
<td>1 month</td>
<td>VPBs, pairs, VT =</td>
</tr>
<tr>
<td>Gurlek*</td>
<td>enalapril</td>
<td>24</td>
<td>NYHA 3</td>
<td>double-blind</td>
<td>4 weeks</td>
<td>VPBs, pairs, VT ↓</td>
</tr>
<tr>
<td>Adgey*</td>
<td>lisinopril</td>
<td>156</td>
<td>NYHA 3-4</td>
<td>blinded data, pre-post</td>
<td>24 weeks</td>
<td>VT ↓</td>
</tr>
<tr>
<td></td>
<td>enalapril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; NYHA, New York Heart Association class. Other abbrevations see Table 1.4.
### Table 1.6. Effect of ACE inhibitors on late ventricular arrhythmias and sudden death

<table>
<thead>
<tr>
<th>Author</th>
<th>Compound</th>
<th>N</th>
<th>Patient selection</th>
<th>Protocol</th>
<th>Follow up</th>
<th>Effect on VAs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sudden death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS²¹⁰</td>
<td>enalapril</td>
<td>253</td>
<td>NYHA 4</td>
<td>vs placebo</td>
<td>6 months</td>
<td>no effect on SCD</td>
</tr>
<tr>
<td>Fonarow²¹¹</td>
<td>captopril</td>
<td>117</td>
<td>NYHA 3-4</td>
<td>vs hydralazine-ISDN</td>
<td>8 months</td>
<td>SCD ↓ 76% (23 - 92)</td>
</tr>
<tr>
<td>Newman²¹²</td>
<td>captopril</td>
<td>105</td>
<td>NYHA 2-3</td>
<td>vs placebo</td>
<td>3 months</td>
<td>SCD ↓ 87% (2 - 98)</td>
</tr>
<tr>
<td>SOLVD I²¹³</td>
<td>enalapril</td>
<td>2569</td>
<td>NYHA 2-3</td>
<td>vs placebo</td>
<td>41 months</td>
<td>SCD ↓ 10% (NS)</td>
</tr>
<tr>
<td>MHFT²⁰⁵</td>
<td>captopril</td>
<td>170</td>
<td>NYHA 2</td>
<td>vs placebo</td>
<td>2.7 years</td>
<td>no effect on SCD</td>
</tr>
<tr>
<td>VHeFT II²¹⁴</td>
<td>enalapril</td>
<td>804</td>
<td>EF &lt; 45%</td>
<td>vs hydralazine-ISDN</td>
<td>2 years</td>
<td>SCD ↓ 35% (6 - 55)</td>
</tr>
<tr>
<td>SOLVD II²¹⁷</td>
<td>enalapril</td>
<td>4228</td>
<td>EF ≤ 35%</td>
<td>vs placebo</td>
<td>37 months</td>
<td>SCD ↓ 7% (NS)</td>
</tr>
<tr>
<td>SAVE²¹⁸</td>
<td>captopril</td>
<td>2231</td>
<td>AMI,EF ≤ 40%</td>
<td>vs placebo</td>
<td>42 months</td>
<td>SCD ↓ 19% (NS)</td>
</tr>
<tr>
<td>SMILE²²⁰</td>
<td>zofenopril</td>
<td>1556</td>
<td>&lt; 24 h AMI</td>
<td>vs placebo</td>
<td>6 weeks</td>
<td>SCD ↓ 63% (NS)</td>
</tr>
<tr>
<td>CONSENSUS II²⁹</td>
<td>enalapril</td>
<td>6090</td>
<td>&lt; 24 h AMI</td>
<td>vs placebo</td>
<td>6 months</td>
<td>no effect on SCD</td>
</tr>
<tr>
<td><strong>Late VAs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Søgaard²²¹</td>
<td>captopril</td>
<td>58</td>
<td>AMI,EF ≤ 45%</td>
<td>vs placebo</td>
<td>6 months</td>
<td>(VPB, pairs, VT) ↓</td>
</tr>
<tr>
<td>SAVE Holter²¹⁹</td>
<td>captopril</td>
<td>553</td>
<td>AMI,EF ≤ 40%</td>
<td>vs placebo</td>
<td>2 years</td>
<td>VT ↓ at 1 year</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; SCD, sudden cardiac death; ISDN, isosorbide dinitrate. Other abbreviations see Table 1.4.
INTRODUCTION

Improve baroreflex sensitivity and heart rate variability after acute myocardial infarction. Both measures indicate that the relative dominance of sympathetic activity is reduced, which may contribute to a reduction of ventricular arrhythmias after myocardial infarction. Another potentially beneficial effect of ACE inhibitors lies in the modulation of low potassium levels. Hypokalemia is an important arrhythmogenic factor after myocardial infarction and is associated with an increased incidence of VF. Underlying mechanisms include slow conduction by hyperpolarization, increased automaticity by increase in the rate of phase 4 depolarization, and induction of afterdepolarizations by reduction of the sodium/calcium exchange mechanism. An increase in potassium levels as a result of ACE inhibition may prevent ventricular arrhythmias provoked by these mechanisms. This may be of special importance in the acute phase of myocardial infarction, when potassium levels are low due to stress and/or diuretic treatment.

Evidence for reduction of late postinfarction arrhythmias in humans

Most evidence concerning the effect of ACE inhibitors on late ventricular arrhythmias is obtained from patients with heart failure, many of whom have left ventricular dysfunction caused by one or more previous myocardial infarction(s). Table 1.5 lists a number of studies investigating the effect of ACE inhibition on ventricular arrhythmias in patients with heart failure. Most of these studies were relatively small and used Holter monitoring to detect ventricular arrhythmias. The ACE inhibitor most frequently used was captopril or enalapril. Most studies had a double-blind, placebo-controlled design, but some open studies have also been reported. The follow-up period varied from 4 weeks to 32 months. Patient selection, protocol, or duration of follow-up did not seem to influence the effect of ACE inhibition on the incidence of ventricular arrhythmias. The majority of these studies showed some reduction of ventricular arrhythmias. However, other studies showing no effect may not have been published.

The effect of ACE inhibitors on sudden cardiac death may also add to the discussion of the anti-arrhythmic effect of these compounds. A number of trials that investigated the effect of ACE inhibitors on total mortality and sudden cardiac death are listed in Table 1.6. The first large trial that studied the effects of ACE inhibition on mortality in patients with serious heart failure (NYHA class IV) was the CONSENSUS study (for NYHA classification, see box on opposite page). This study demonstrated a beneficial effect of enalapril on total mortality, but not on sudden cardiac death. Fonarow et al. compared the effects of Hydralazine combined with isosorbide dinitrate with Captopril in 117
patients evaluated for cardiac transplantation (the Hy-C trial). Despite similar hemodynamic effects, sudden cardiac death occurred more often in the hydralazine-isosorbide dinitrate group (28% vs 7%). Newman et al.\textsuperscript{212} described a clear reduction in mortality in 105 patients with moderate to severe heart failure treated with captopril or placebo. Of the 11 patients that died, 8 died suddenly and thus an effect on arrhythmogenic death was suspected. In contrast, the Studies Of Left Ventricular Dysfunction (SOLVD) investigators,\textsuperscript{213} who investigated patients with an ejection fraction of less than or equal to 35% and signs of heart failure (treatment arm, SOLVD I), showed an effect of enalapril on total mortality compared to placebo but not on sudden cardiac death. Similar to the studies by Fonarow et al. and Newman et al., most of the patients in this study were in NYHA heart failure classes II and III. The Munich mild Heart Failure Trial (MHFT), investigating 170 patients with only mild signs of heart failure (NYHA class II), found no difference in sudden death after 2.7 years of follow up between patients treated with captopril or placebo. In the second Veterans administration cooperative vasodilator Heart Failure Trial (VHeFT II),\textsuperscript{214} Cohn et al. compared the effects of hydralazine-isosorbide dinitrate therapy with enalapril therapy in patients with a reduced ejection fraction (< 45%). Most patients were in NYHA class II or III. A significant reduction of sudden cardiac death was found in the enalapril group. In addition, this finding was paralleled by a reduction in VT detected during 4-hour to 8-hour Holter monitoring after three months and after one and two years.\textsuperscript{215} It is important to note that the frequency of VT in the hydralazine-isosorbide dinitrate group was similar to the incidence of VT in the placebo group of the VHeFT I study,\textsuperscript{216} which had identical entry criteria as VHeFT I. In SOLVD II (prevention arm),\textsuperscript{217} patients with a reduced ejection fraction but no overt heart failure were investigated. In this study, 80% of the patients had had a myocardial infarction before study entry.
A small, not statistically significant reduction of sudden cardiac death was observed in patients treated with enalapril. The SAVE study\textsuperscript{218} also investigated patients with a reduced ejection fraction (40% or less) and no symptoms of heart failure (NYHA class I). However, in contrast to SOLVD II, where patients with recent myocardial infarction were excluded, SAVE patients were randomized 3-16 days after acute myocardial infarction. Although sudden death was reduced by 19\% (similar to the effect on total mortality), this finding did not reach statistical significance. The SAVE investigators did observe a reduction of VT during Holter monitoring at one year, but not at two years, in patients treated with captopril.\textsuperscript{219} In the SMILE study,\textsuperscript{220} the effect of zofenopril on mortality was investigated in patients with anterior wall myocardial infarction who were not eligible for thrombolytic therapy. Patients were treated within 24 hours after the onset of symptoms. After six weeks, four patients had died suddenly in the zofenopril group, compared to 11 in the placebo group (p-value not significant). The SMILE investigators did observe a significant reduction of total mortality. In CONSENSUS II\textsuperscript{179} more than 6000 patients with acute myocardial infarction were randomly assigned to i.v. enalapril or placebo therapy within 24 hours of symptom onset. Of all patients, 56\% received thrombolytic therapy. There was no difference in the incidence of sudden cardiac death after 6 months (2.8\% vs 2.9\%, in the treated vs the nontreated group, respectively). Finally, in a recent study, Søgaard et al.\textsuperscript{221} described the incidence of ventricular arrhythmias during 24-hour Holter monitoring in 56 patients with a reduced ejection fraction (≤ 45\%) but no overt heart failure after acute myocardial infarction. During six months of follow up, an increase in ventricular arrhythmias in the placebo group

### NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS

I. Patients without limitation of physical activity. Ordinary activity does not cause undo fatigue, dyspnea or angina pain.

II. Patients with slight (IIS) or moderate (IIM) limitation of physical activity who are comfortable at rest.

III. Patients with marked limitation of physical activity who are comfortable at rest.

IV. Patients with inability to carry on any physical activity without discomfort. Symptoms may be present at rest.
was observed, compared to a decrease in the captopril group resulting in a significant difference at 180 days.

In summary, most studies investigating the effects of ACE inhibition in patients with heart failure do report on a beneficial effect on either or both sudden cardiac death and ventricular arrhythmias. However, this effect does not always reach statistical significance. This finding may result from the use of different definitions of sudden cardiac death or from differences in study design and patient selection. In patients with recent myocardial infarction, a reduced incidence of ventricular arrhythmias has only been reported in patients with significant left ventricular dysfunction. In patients with relatively preserved left ventricular function, there has been no report of a reduction of ventricular arrhythmias.

§ 7. Aims of the thesis

In Figure 1.3, the issues that are addressed in this thesis are depicted. In the following chapter, chapter 2, the association between dilatation of the left ventricle and the occurrence of ventricular arrhythmias is described. In chapters 3 and 4, the possible underlying electrophysiological mechanisms of this association are investigated using body surface mapping (chapter 3) and signal-averaged electrocardiography (chapter 4). In chapter 5, the role of early sympathetic activity, quantified by norepinephrine levels, in the occurrence of early and late ventricular arrhythmias is discussed. In the same chapter, the effect of successful reperfusion on norepinephrine levels and ventricular arrhythmias is addressed.
In chapter 6, the interaction of neurohumoral activation, quantified as heart rate variability, and left ventricular dilatation is described. In chapter 7, we evaluate the effects of ACE inhibition on dilatation, neurohumoral activation, and ventricular arrhythmias up to three months after myocardial infarction. In chapter 8, focus is on the effects of ACE inhibition on left ventricular dilatation and congestive heart failure up to 12 months after myocardial infarction. In chapter 9, the effects of ACE inhibition on ventricular arrhythmias requiring treatment is described. Finally, in chapter 10 our findings in CATS are summarized and commented.

In brief, the aims of this thesis were to address the following questions:

1) does ACE inhibition, administered during thrombolysis, reduce ventricular arrhythmias early after myocardial infarction, and if so, which mechanisms are...
operative?

2) What is the role of left ventricular dilatation and neurohumoral activation in the cause of ventricular arrhythmias after thrombolytic therapy, and, in the case of left ventricular dilatation, to what extent are slow conduction and dispersion in refractoriness explanatory mechanisms?

3) Can ACE inhibition modify these arrhythmogenic factors, and does this result in a reduction of late ventricular arrhythmias?

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INTRODUCTION


CHAPTER 1


INTRODUCTION


CHAPTER 1

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CHAPTER 1


INTRODUCTION


CHAPTER 1


INTRODUCTION


