Cardiogenic shock complicating acute myocardial infarction

Prognostic impact of early and late shock development

M.G. Lindholm\textsuperscript{a}, L. Køber\textsuperscript{a}, S. Boesgaard\textsuperscript{a}, C. Torp-Pedersen\textsuperscript{b}, J. Aldershvile\textsuperscript{a}\textsuperscript{*}, on behalf of the TRACE study group

\textsuperscript{a}Medical Department B 2142, Division of Cardiology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK 2100, Copenhagen, Denmark
\textsuperscript{b}Department of Cardiology, Gentofte University Hospital, Copenhagen, Denmark

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Aims Cardiogenic shock accounts for the majority of deaths following acute myocardial infarction. The majority of outcome data on this issue are, however, derived from single hospitals, referral centers or selected patients in randomized studies. The purpose of this study was to investigate incidence, outcome and prognostic significance of cardiogenic shock in 6676 consecutive patients with acute myocardial infarction.

Methods and results Demographic and clinical data including the presence of cardiogenic shock were prospectively collected in 6676 non-invasively managed patients with myocardial infarction consecutively admitted to 27 different hospitals during a 2-year period. Six-year mortality data were collected in 99.9% of the population. Cardiogenic shock developed in 444 patients (6.7%). In 59% of these patients cardiogenic shock developed within 48 h, 11% developed shock during days 3 and 4 and 30% later than 4 days after the infarction. Thirty-day and 6-year mortality was 62 and 88% among shock patients compared to 9 and 45% in non-shock patients. Patients with early shock development (days 1–2) had a significantly lower 30-day mortality (45%) than those with intermediate or late shock development (>80%) (P<0.05). In 30-day survivors, survival the following years was lower than in patients without cardiogenic shock but with post-infarction heart failure.

Conclusions In this nationwide prospectively collected registry, non-invasively managed consecutive myocardial infarct patients with cardiogenic shock had an extremely reduced life expectancy. Every attempt to improve treatment, prevention and identification of patients at risk of shock development should be strongly encouraged.

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KEYWORDS
Cardiogenic shock;
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Prognosis;
Survival

Introduction

Although the treatment of acute myocardial infarction and chronic heart failure has improved considerably over the last 40 years, the mortality of patients in cardiogenic shock complicating myocardial infarction remains extremely high and has not changed in recent decades\textsuperscript{1}. Five to 10% of patients with myocardial infarction develop cardiogenic shock and 2/3 of these patients are expected to die within a few weeks.\textsuperscript{1–3} Modern intensive care treatment has not been shown to improve survival and
although the incidence of shock is reduced in thrombolyzed patients, even the effect of thrombolytics is limited in fully developed cardiogenic shock.\textsuperscript{4,5} Nevertheless, recent data suggest that the mortality from cardiogenic shock is declining, simultaneously with the current implementation of a more invasive strategy for the treatment of cardiogenic shock in patients with acute myocardial infarction.\textsuperscript{3,6,7}

With an increasing interest in an aggressive approach to cardiogenic shock it is important to understand interventional studies in an appropriate epidemiological framework. The majority of available data, in particular those obtained after the introduction of thrombolytic therapy, are from single hospitals, referral centers or the selected patients in a randomized study. For this reason we have analysed risk factors for cardiogenic shock and its prognostic importance in 6676 consecutive acute myocardial infarct patients who received contemporary non-invasive treatment. There has been particular emphasis on the timing of cardiogenic shock in relation to the infarction. Therefore, this study describes the incidence and short- and long-term outcome of patients in cardiogenic shock depending on whether shock developed early or late after the myocardial infarction.

Patients and methods

Study population and design

Details of the Trandolapril Cardiac Evaluation (TRACE) protocol have been published elsewhere.\textsuperscript{8,9} TRACE was a multicenter, nationwide, double-blind, placebo-controlled, parallel group study conducted in 27 centers in Denmark.

All patients with a myocardial infarction admitted to the 27 departments were screened for entry, and data from this screening form the basis of the TRACE registry used in the present study. From May 1990 to July 1992 consecutive male and female patients over the age of 18 years with an enzyme-confirmed myocardial infarction were registered. A medical history as well as in-hospital complications were systematically recorded. If a patient screened for entry into the TRACE study was not included in the study, the patient could be re-screened later if admitted with a new infarction. As a consequence, the 7001 consecutive cases in the TRACE registry represent 6676 patients. For the purpose of the current investigation each patient was included only once in the analyses using the first myocardial infarction of the study period. Thus this study included 6676 consecutively admitted patients with a myocardial infarction.

Acute myocardial infarction was defined as chest discomfort and/or specific electrocardiographic changes accompanied by elevation of cardiac enzymes to at least twice the upper normal value. The timing of myocardial infarction was determined in relation to onset of symptoms. For the purpose of the present study cardiogenic shock was defined as the presence or development of Killip class IV heart failure. The definition of cardiogenic shock was based on systemic hypotension, symptoms of vital organ hypoperfusion (oliguria, change in mental status, cold extremities) and perceived by the investigator to be caused by a low cardiac output state. Thus, the definition did not require measurement of cardiac index or pulmonary capillary wedge pressure. The cause of cardiogenic shock was not separated in the TRACE registry. Thus a distinction between cardiogenic shock caused by ventricular dysfunction or a mechanical complication (ventricular septal defect, papillary muscle rupture or severe mitral regurgitation) is not possible. All patients were classified according to Killip class during the period days 1–2 (0–48 h, early shock), days 3–4 (intermediate), and day +4 (late shock). Heart failure without cardiogenic shock was defined as a history of heart failure requiring diuretic treatment and/or Killip class II–III during hospital stay. Patients with only transient signs of heart failure are also included.

Data collection

Demographic, medical and laboratory variables were collected from each of the 27 centers, regardless of whether the patients were included in the final TRACE study. Mortality data were obtained electronically from the Danish Central Person register in June 1998. Data from 28 non-Danish residents and three Danish patients with missing data were censored at the time of discharge from hospital. Eight patients were lost to follow up during the course of the study (emigration) and their survival data were censored at the time when they were last known to be alive.

Statistical analysis

Characteristics of the myocardial infarction population were analysed using the chi-square test for discrete variables and the Kruskal–Wallis test for continuous variables. Kaplan–Meier curves were obtained and comparisons of mortality from all
causes were made with the log–rank test. Relative risk and associated 95% confidence intervals were calculated as hazard ratios derived from the Cox proportional-hazards regression model. In the models performed to study the importance of the time of cardiogenic shock development, separate cardiogenic shock variables were defined according to selected time periods. These variables were all entered into the same proportional hazard model as time-dependent variables. Calculations were performed using the SAS statistical package. Two-sided \( P \) values with a significance level of 0.05 were calculated.

**Results**

In six patients development of cardiogenic shock could not be evaluated. Thus, baseline characteristics for the 6670 patients included are shown in Table 1. Cardiogenic shock was present in 444 patients, corresponding to an incidence of 6.7%. Of the 444 patients with cardiogenic shock 59% \( (n=263) \) had an early, 11% \( (n=49) \) had an intermediate and 30% \( (n=132) \) had late development of cardiogenic shock. Patients developing cardiogenic shock were about 5 years older than those without shock.

Among the classical risk factors in relation to ischaemic heart disease, diabetes, angina and previous myocardial infarction were more common in the group of patients with cardiogenic shock. In addition, a history of heart failure was twice as prevalent among the shock patients. As expected, thrombolytic therapy had been used less in the shock population as compared to the non-shock patients, reflecting that patients not being revascularized are at higher risk of developing cardiogenic shock. Anterior Q-wave myocardial infarction and bundle branch block were more common in the shock population, whereas the presence of inferior myocardial infarction and ST-segment elevation did not differ between the groups.

As shown in Table 2, there are important differences between patients developing shock early and late. Thrombolytics were used less frequently in patients developing late shock, and female sex was more common in late as compared to early shock development. Trends towards a more frequent appearance in late as compared to early cardiogenic shock was found for patients with a history of heart failure or diabetes or the presence of anterior Q-wave myocardial infarction.

Factors related to the relative risk of dying when admitted with acute myocardial infarction are shown in Table 3. Well-known risk factors such as diabetes, hypertension, heart failure, and angina are all of significance, whereas previous myocardial infarction had no influence in the present population. In addition thrombolytic therapy reduced the risk of dying significantly. Both increasing age and female sex carried a small but significant increased risk. There were major changes in the risk ratio in patients who had a re-infarction during the in-hospital period, but development of cardiogenic shock carried the single most important risk of dying with a risk ratio of nearly 2.6 and a CI from 2.3–3.0.

### Table 1  Baseline characteristics in consecutive patients with acute myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>All ( n=6670 )</th>
<th>Cardiogenic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent ( n=6226 )</td>
<td>Present ( n=444 )</td>
</tr>
<tr>
<td>Age (69 (47–84)</td>
<td>68 (46–84)</td>
<td>74 (54–87)</td>
</tr>
<tr>
<td>Sex (male) 67%</td>
<td>68%</td>
<td>60%</td>
</tr>
<tr>
<td>History of Hypertension 23%</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>Angina 37%</td>
<td>36%</td>
<td>44%</td>
</tr>
<tr>
<td>Previous MI 23%</td>
<td>23%</td>
<td>29%</td>
</tr>
<tr>
<td>Diabetes 11%</td>
<td>10%</td>
<td>17%</td>
</tr>
<tr>
<td>Heart failure 17%</td>
<td>16%</td>
<td>32%</td>
</tr>
<tr>
<td>Thrombolysis 41%</td>
<td>42%</td>
<td>25%</td>
</tr>
<tr>
<td>Anterior Q-wave MI 26%</td>
<td>26%</td>
<td>31%</td>
</tr>
<tr>
<td>Inferior Q-wave MI 31%</td>
<td>31%</td>
<td>27%</td>
</tr>
<tr>
<td>ST-segment elevation 64%</td>
<td>64%</td>
<td>62%</td>
</tr>
<tr>
<td>Bundle branch block 8%</td>
<td>7%</td>
<td>17%</td>
</tr>
<tr>
<td>In-hospital reinfarction 3%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Heart failure 54%</td>
<td>50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*\( P \)-values are obtained by comparing patients with cardiogenic shock to the ones without cardiogenic shock. Continuous variables are given as median (5–95 percentiles). MI=myocardial infarction.*
Fig. 1 shows mortality for up to 7 years after the myocardial infarction for patients with and without cardiogenic shock (missing survival data in two patients). Thirty-day mortality was 62% among patients with cardiogenic shock as compared to 9% among non-shock patients. When subdividing patients with cardiogenic shock according to the time elapsed from index myocardial infarction to development of shock, a marked difference in survival appeared (Fig. 2). Patients with an early development of shock had a 30-day mortality of 45% compared to 84 and 87%, respectively, among those with an intermediate and late development of shock. Using univariate analysis, risk ratios for the three groups were 3.4, 9.5, and 16.5 (CI 2.9–3.8,
7.0–12.9, and 13.4–20.4) \((P<0.0001)\). In addition, using multivariate analysis the relative risk ratios were 1.8, 6.0, and 7.2 (CI 1.5–2.1, 4.1–8.7, and 5.7–9.0), again highly significant \((P<0.0001)\).

Six-year mortality (Figs. 1 and 2) was 45% in myocardial infarction patients without cardiogenic shock and 88% in the group of patients with cardiogenic shock. In absolute numbers, only three and one, respectively, of the patients with intermediate or late cardiogenic shock development were alive after 5 years, stressing the serious prognosis of these patients. Fig. 3 shows survival curves for patients alive after 30 days. The figure illustrates survival of patients with cardiogenic shock compared to patients with and without heart failure at the initial hospitalization. The long-term prognosis for patients with cardiogenic shock alive after 30 days is significantly \((P<0.05)\) worse (6-year mortality 68%) than that seen among non-cardiogenic shock patients with heart failure (6-year mortality 40%) during their hospitalization.

Discussion

This study shows that the time interval between myocardial infarction and development of cardiogenic shock is a major determinant of mortality in patients with cardiogenic shock complicating myocardial infarction. Thirty-day mortality was 45% in patients with early shock as compared to more than 80% in patients developing cardiogenic shock more than 48 h after a myocardial infarction.

Cardiogenic shock populations

The TRACE registry includes 6676 patients with myocardial infarction consecutively admitted to 27 Danish departments during the period 1990–92 and we are able to show data on 99.9%. Treatment strategies at that time were based on thrombolytic therapy and inotropic support, and early mechanical revascularization or intra-aortic balloon counterpulsation was not used. The incidence of shock was 6.7%, which is very similar to the results in the Global Utilization of Steptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial (7.2%), and a recently published population based study (7.1%).\(^1\)\(^2\) Several other
characteristics from this latter study\textsuperscript{1} are in agreement with the present findings. In both studies the typical patient with cardiogenic shock is male, slightly older than the non-cardiogenic shock patient, with more risk factors and an anterior myocardial infarction. Additionally, the mean age of the total myocardial infarction population is 69–70 years and in-hospital/30-day mortality in non-shock patients approximately 10% in both studies. In 1993, 61% of patients with cardiogenic shock died in the American study as compared to 62% in the present study. Thus, the present population appears to be representative, in terms of cardiogenic shock, of a myocardial infarction cohort in an industrialised western society. Similarly, the 1-year mortality of the entire cohort of patients is exactly the same as found by McGovern et al. during the same time period (comparison includes only patients younger than 75 years of age, as older patients were not available in the Minnesota Heart study).\textsuperscript{9}

Early and late cardiogenic shock

Data on the prognostic implications of the timing of onset of cardiogenic shock after myocardial infarction are very limited and this study is the first to systematically address this issue in an unselected population of myocardial infarct patients. In the present study, 59% of cardiogenic shock patients had early shock (0–48 h after myocardial infarction), 11% developed shock at 3–4 days and 30% at 5 days or more after the index myocardial infarction. In a selected group of 845 infarct patients not presenting with cardiogenic shock, Hands et al.\textsuperscript{10} reported that 50% of the episodes of cardiogenic shock occurred later than 24 h after admission. Data from the GUSTO-1 trial\textsuperscript{2} and from the SHOCK-trial registry\textsuperscript{11} suggest that cardiogenic shock primarily is a very early (75% <24 h) event. However, the GUSTO-1 trial\textsuperscript{2} reported on cardiogenic shock development among thrombolytic eligible patients and the SHOCK (should we emergently revascularize occluded coronaries for cardiogenic shock) trial registry\textsuperscript{11} only includes patients with cardiogenic shock primarily due to left ventricular (LV) failure. Another likely explanation of the late appearance of cardiogenic shock in this study relates to the fact that 38% of the cardiogenic shock patients had a non ST-elevation myocardial infarction. This condition is associated with late appearance of cardiogenic shock (median 76 h) as compared to ST elevation myocardial infarction.\textsuperscript{12–14} Differences between the studies may also exist due to the definition of cardiogenic shock. In the present study cardiogenic shock was defined as the presence of Killip class IV and a recent study shows\textsuperscript{15} that cardiogenic shock may also be present in patients not fulfilling this criterion.

Patients who developed cardiogenic shock had a higher rate of conventional myocardial infarction-related risk factors than non-cardiogenic shock patients. Female sex, less use of thrombolytics and in-hospital re-infarction were significant characteristics of the group of patients with late development of cardiogenic shock. The latter finding is in accordance with previous findings.\textsuperscript{11} Within the total myocardial infarction population in the present study, 30-day mortality was 12.5% and in a multivariate analysis cardiogenic shock, in-hospital reinfarction and a history of diabetes and heart failure were all strong predictors of death. In contrast an inverse relationship was found for thrombolytic therapy.

Cardiogenic shock mortality

The overall 30-day mortality rate of 62% is in accordance with major recent reports\textsuperscript{1,2} showing in-hospital mortality rates of 61% (1993 data) and 30-day mortality of 55%, respectively. Corresponding values in the SHOCK trial (where all patients had early shock) and the SHOCK-trial registry were 56 and 60% for patients with ventricular dysfunction without mechanical complications.\textsuperscript{3} Patients developing shock earlier than 48 h had a 30-day mortality of 45% as compared to patients with later shock who had a mortality of more than 84%. The 45% mortality rate in patients with early shock is lower than recently reported.\textsuperscript{3} According to two recent studies as many as 11–25% of cardiogenic shock patients have shock on arrival.\textsuperscript{2,16} A number of these patients may have died before a myocardial infarction could be verified and may therefore not have been included in present study. It is also possible that the non-invasive/clinical criteria for cardiogenic shock in the present study may have resulted in inclusion of a slightly different population than in the SHOCK trial.\textsuperscript{3} However, it is important to stress that the present data on early shock suggest that patients enrolled in the randomized SHOCK trial\textsuperscript{3} apparently do not represent a selected group of low-risk cardiogenic shock patients.

Recent data suggest that cardiogenic shock following a non-ST elevation myocardial infarction is associated with a very high mortality of 77%.\textsuperscript{13} In the present study recurrent ischemia and re-infarction may also be of importance in relation to the outcome of late shock. In-hospital re-infarction increased from 3% in early shock to 20% in late
shock (>4 days) and re-infarction was an important predictor of death with an odds ratio of 1.9 (CI: 1.6–2.3). Although the re-infarction rate did not differ between shock developed before and after 24 h in the SHOCK registry,11 recurrent ischemia was more frequent in late as compared to early shock (38 and 13%, respectively) and these patients were more likely to undergo late revascularization than patients in the present study. Thus, consideration should be given to whether patients with cardiogenic shock caused by re-infarction, recurrent ischemia or non-ST elevation myocardial infarction constitute a subgroup, requiring the narrow time-span for revascularization between myocardial infarction and cardiogenic shock used in the SHOCK trial to be extended.

Finally, this study demonstrates for the first time long-term survival (more than 5-years) in patients with cardiogenic shock. Since less than 15% of cardiogenic shock patients were alive after 6 years, this study confirms that cardiogenic shock continues to be a very serious clinical event. In fact, almost all patients with intermediate or late development of cardiogenic shock died within 5 years. Patients surviving 30 days had a mortality rate slightly worse than patients with myocardial infarction and an in-hospital diagnosis of heart failure. The consequences of modern heart failure therapy and revascularization in this population are unknown, but data from the SHOCK trial suggest that early revascularization may improve the long-term prognosis in patients with cardiogenic shock development.17

Conclusions

This study demonstrates that the timing of cardiogenic shock after onset of myocardial infarction provides important prognostic information. In 444 consecutive and not mechanically revascularized patients with cardiogenic shock complicating myocardial infarction, development of shock later than 48 h after myocardial infarction carries an extremely high 30-day mortality (>80%). Patients alive after 30 days have a long-term survival rate that is moderately worse than myocardial infarction patients with heart failure. Thus, data from this nationwide study confirm that medical therapy alone does not result in an acceptable outcome for patients with cardiogenic shock complicating acute myocardial infarction.

Acknowledgement

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