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Factors related to prehospital delay in patients with ST-elevation myocardial infarction

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Summary

Acute myocardial infarction (AMI) is one of the leading causes of death across the world. Due to the highly time dependent nature of the thrombolysis treatment for reducing myocardial necrosis, efforts has been made to reduce the time interval between symptoms onset and receiving treatment. During last decade, progress has been achieved to reduce in-hospital delay. However, the major component of the delay time-patients' decision delay remain largely unchanged. Mass media campaign for enhancing people's AMI knowledge failed to change patients' behavior during the acute symptom onset. Based on the previous evidences, factors associated with pre-hospital delay can be categorized into four aspects: social demographic factors; clinical factors; knowledge, appraisal and behavioral factors and psychological factors. Among them, appraisal and behavioral factors and psychological factors take the dominant influence on delay time.

The present doctoral thesis outlines two articles, which are based on data from the multicentre, cross-sectional MEDEA study (Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction). The study provided a homogenous recruitment and data collection methods. The first article investigated the impact of denial on prehosptial delay and patients' cognitive and behavior responses during the acute situation. Counterintuitively, denial exhibited a minimal impact on delay and patients' behavioral response during symptom onset. Moreover, denial even exhibited a protective effect of buffering patients' negative affectivity before and during the acute events. The second article sought to identify the impact of generalized anxiety disorder (GAD) on patients' delay time. Surprisingly, GAD played as a protective factor in this acute situation which urge the patients to seek help and thus reduced the chance of delay longer than two hours. However, as has been well established, GAD was associated with depression, vital exhaustion and suboptimal well-being. GAD here might work as a double edged sword which reduce the time for patients to seek help but might also potentially impaired the quality of life of the patients in a long term.

The doctor thesis has clarified the most common suspects of physician for the psychological reason causing delay and reflected that sometimes negative emotions or maladaptive coping mechanism can be utilized to trigger adequate help seeking behavior during acute situation. Further intervention should focus more on patients‘ cognitive responses to the symptom onset. General physicians as the group who closely work with the patients might also be able to conduct more individualized intervention to the patients with high risk of AMI.

Zusammenfassung

Der akute Myokardinfarkt (AMI) ist eine der häufigsten Todesursachen weltweit. Da die Behandlung einer Thrombolyse zur Reduktion einer Herzmuskelnekrose stark zeitabhängig ist wurden Anstrengungen unternommen, um das Zeitintervall zwischen Symptombeginn und der eigentlichen Behandlung zu reduzieren. Im letzten Jahrzehnt wurden Fortschritte erzielt, um Verzögerungen innerhalb von Krankenhäusern zu reduzieren. Die Hauptkomponente der Verzögerungszeit – die Entscheidungsverzögerung durch Patienten - bleibt jedoch weitgehend unverändert. Groß angelegte Medienkampagnen zur Verbesserung des allgemeinen AMI-Wissens brachten keine Veränderung hinsichtlich des Verhaltens der Patienten während dem Eintreten akuter Symptome. Basierend auf den bisherigen Erkenntnissen können die mit der Verzögerung vor der Krankenhauseinlieferung verbundenen Faktoren in vier Aspekte unterteilt werden: sozial-demografische Faktoren, klinische Faktoren, Wissens-, Bewertungs- und Verhaltensfaktoren sowie psychologische Faktoren, wobei Bewertungs - und Verhaltensfaktoren sowie psychologische Faktoren die Verzögerungszeit am schwerwiegendsten beeinflussen.

Die vorliegende Dissertation umfasst zwei Manuskripte!, die auf Daten der multizentrischen Querschnittsstudie MEDEA (Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction) basieren. Die Studie bot eine einheitliche Rekrutierungs- und Datenerhebungsmethode.

Das ersteManuskript untersuchte die Auswirkungen von Verleugnung auf die prehospitale Verzögerung sowie die kognitiven und verhaltensbedingten Reaktionen der Patienten während der akuten Situation. Überraschenderweise zeigte die Verleugnung einen minimalen Einfluss auf die Verzögerung sowie die verhaltensbedingten Reaktionen der Patienten während des Symptombeginns. Darüber hinaus zeigte Verleugnung sogar insofern eine schützende Wirkung, dass negative Affektivität der Patienten vor und während des akuten Ereignisses abgemildert wurden.

Im zweiten Artikel wurde versucht, die Auswirkungen einer generalisierten Angststörung (GAD) auf die Verzögerungszeit von Patienten zu ermitteln.

Überraschenderweise nahmen Angststörungen in der akuten Situation eine Schutzfunktion ein, welche die Patienten dazu drängte, Hilfe zu suchen und dadurch die Wahrscheinlichkeit einer Verzögerung um mehr als zwei Stunden verringerte. Wie jedoch bereits mehrfach aufgezeigt, konnten Angststörungen mit Depressionen, vitaler Erschöpfung und suboptimalem Wohlbefinden in Verbindung gebracht werden. Angststörungen könnten hier als zweischneidiges Schwert wirken, indem zum einen die Zeit Hilfe zu suchen verringert wird, zum anderen aber möglicherweise auch die Lebensqualität der Patienten langfristig beeinträchtigen werden kann.

Die Doktorarbeit hat die von Ärzten am häufigsten vermuteten Einflussfaktoren hinsichtlich psychologischen Verzögerungsfaktoren aufgezeigt und darauf hingewiesen, dass negative Emotionen oder maladaptive Bewältigungsmechanismen dazu genutzt werden können, um in akuten Situationen ein adäquates Hilfesuchverhalten auszulösen. Weitere Interventionen sollten sich stärker auf die kognitiven Reaktionen der Patienten hinsichtlich des Auftretens der Symptome konzentrieren. Allgemeinmediziner als die Gruppe, die eng mit den Patienten zusammenarbeitet, können möglicherweise auch stärker individualisierte Eingriffe bei Patienten mit hohem AMI-Risiko durchführen.

Abbreviations

AMI	Acute Myocardial Infarction
STEMI	ST segment Elevation Myocardial Infarction
PHD	Prehospital Delay
MEDEA	Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction
GAD	Generalized Anxiety Disorder
CHD	Coronary Heart Disease
MACE	Major Adverse Cardiac Event
ECG	Electrocardiogram
PCI	primary percutaneous coronary intervention

The present doctoral thesis is divided into four main sections. The introduction covers background information on pre-hospital delay for myocardial infarction patients. In the second chapter, background information is given on mental health aspects relevant to prehospital delay. The third chapter outlines the rational and methods of the thesis. Here, data, aims and methods are described in detail. Chapter 4 provides a detailed summary of the results of the manuscripts and chapter 5 contains discussion and conclusions derived from the results

Chapter 1.Introduction: Prehospital delay of AMI patients: definition and epidemiology

1.1.1 Acute myocardial infarction definition

Acute myocardial infarction (AMI) is defined as the myocardial necrosis in a clinical setting consistent with myocardial ischemia. Patients presenting with ischemic symptoms, consistent ST-segment elevation on the electrocardiogram (ECG) and an elevation of biomarkers of myocardial can be diagnosed with AMI.[1]

Typical AMI symptoms include chest pain radiating into the neck, shoulder, or arm, lasting more than 30 minutes, and not relieved by nitroglycerin, may or may not accompanied by dyspnea, diaphoresis, weakness, and nausea. The electrocardiogram shows ST-segment elevation (later changing to depression) and T-wave inversion in leads reflects the area of infarction. Q waves indicate transmural damage and a poorer prognosis. Myocardial biomarkers inserum include myoglobin,

the MB isoensyme of creatinekinase, and troponings. The diagnosis is confirmed by the imaging evidence of new loss of viable myocardium, or newly detected regional wall motion abnormality with identification of an intracoronary thrombus by angiography or autopsy.

1.1.2 Classifications of myocardial infarction:

There are two types of myocardial infarction: ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (N-STEMI). The differences are based on whether an ST section of the tracing is higher than the baseline or not. In the present doctoral thesis, the study population are restricted to patients with STEMI

1.1.3 Epidemiology:

Ischemic heart disease is still the leading cause of death with an increasing prevalence worldwide.[1] In Europe, a large scale of spatial gradient within Europe still exists. The burden of ischemic cardiac diseases is significantly higher in Eastern Europe. As one of the most comprehensive STEMI registry [2], the incidence in Sweden is 66 per 100 000 person year, similar with the numbers in the Czech Republic, Belgium, and the USA[3]. In other European countries, the incidence rate ranged from 43 to 144 per 100 000 person year[4]. A declining trend in the incidence of STEMI has been reported meanwhile an increasing in NSTEMI has also been

found[1]. In Germany, there was a significant average yearly decline of STEMI about 1.6% from 1990 to 2011[5] .

Several recent studies have addressed a decrease in acute and long-term mortality following STEMI due to the wild application of reperfusion therapy including primary percutaneous coronary intervention (PCI), modern antithrombotic therapy and secondary prevention treatment[6]. Nevertheless, mortality still remains approximately 12% of patients dead within 6 months[7], but with higher mortality rates in older individuals and women[8]. Up to one half of patients with AMI died before reaching the hospital, with men more likely to die out of hospital than women.

1.1.4 Treatment of AMI

Since the thrombolysis and angioplasty been introduced in the early 1980s, they have revolutionized the treatment of acute myocardial infarction. Angioplasty (a mechanical treatment) open occluded or partially occluded coronary arteries and thrombolytics dissolving the clot and restoring blood flow to the myocardium. Large clinical trials[9] have demonstrated the effectiveness of both of the treatment in reducing mortlity and improving patients‘ prognosis. Whereas, the effect of the treatment is highly time dependent[10]. The improvement of the cardiac function is inversely related to the time period between symptoms onset and the arrival of the hospital[11]. It has been well-established that longer prehospital delay was associated with higher mortality[12]. To moderate the front wave of necrosis expanding from endocardium faced by infarct artery, timely reperfusion of infarcted artery is the fundamental treatment for intervening the progression of necrosis and salvaging

myocardium[12]

Zahn et al[13] reported in a Germany reigistry data with 7552 AMI patients that thrombolysis was independently associated with a higher mortality rate compared with primary angioplasty in patients delay longer than three hours.

1.1.5 Pre-hospital delay

Given the time dependency nature of the thrombolitic treatment, the importance of reducing time to treatment has been long emphasized in the previous study.[14] Recent guidelines[1,15] recommended a delay of less than 60 minutes between the onset of symptoms and administration of thrombolytic therapy. The time to treatment is composed of two part: “door to needle time“ and “door to bollon time“. Prehosptial delay refers to the door to needle time which can be further divided into decision time, time to initiate medical contact and transportation time. It has been proved that the systemic delay including in-hospital stage and transportation has been optimized since decades.[16]

However, decision time which is the time taken by individuals to interpret their symptoms as cardiac in origin and decide to seek medical help has been found to be the longest phase of delay[17].

Three large-scale studies[18-20] shows only 22%-44% of the patients actually arrive the hospital with in two hours after the onset of the symptoms. KORA-MONICA registry[21] showed that 40% of AMI patients have a prehospital time longer than four hours; even when using a six-hour criterion, 25% to 33% of patients still arrive at the hospital too late.[22] There were even 10 to 20% of the patients delayed longer than 12 hours. International studies have shown a wide variance, range from a few minutes

to several days, and are skewed towards longer delay times.[23]

Althought many hospitals and health regions have put systems in place to expedite drug administration once the patient has sought medical assistance of prehospital delay, delay time remain largely unchanged world-widely since decades. Several large scale registry studies in American shows no improvement of delay time between 90s and 00s [22]. A most recent retrospective study including 2203 patients who underwent primary percutaneous coronary intervention (PCI) between 2008 and 2016 shows a incresing of patients delay less than 2 hours and a reduction in patients delay longer than 6 hours.[24]

Despite annual nationwide campaigns [25,26] of national heart foundations and other cardiac health care providers in many high income countries to improve knowledge on symptoms and adequate health care utilization (e.g. call emergency center or call an ambulance) in the general public, patients still failed to change their help seeking behavior during acute phase of AMI. Mooney et al [27]reviewed the eight interventions aimed at reducing pre-hospital delay time since 1986 and found that the mass media campaign did raise the public awareness of AMI but failed to altering adequate behavior. The knowledge–behaviour gap is well-documented. They further conducted a randomized trial to reduce delay and achieved a significant reduction of delay time by addressing the patients cognitive responses to the symptoms but still were unsuccessful in increasing the use of ambulance. [28]

Chapter 2. Introduction: Factors associated with delay in AMI patients

Since the pre-hospital delay was proved to be the major barrier for AMI patients to achieve the optimum effect of thrombolysis, efforts has been made to investigate and clarify the factors related to pre-hospital delay time in AMI patients presented to the emergency department. To sum up the findings from previous investigations, the main predictors of pre-hospital delay can be grouped into four categories: social demographic factors; clinical factors; knowledge, appraisal and behavioral factors and psychological factors. [11]

2.1.1 Social demographic factors

Female sex and old age are widely acknowledged as major key factors contributing to a longer prehospital delay. A systematic review on this topic disclosed that female sex and old age were significant contributors to substantial delay of arrival[29]. Several large scale longitudinal studies[21] revealed that advanced age remain to be one of the major factors associated with delay and have not changed appreciably over time. A large scale AMI registry including more than 3000 patients[30] found a longer delay in older patients and a dose-response relationship between age and delay time: 4.1 hours in patients <55 years old, 5.2 hours in those 55-64 years old, 5.1 hours in those 65-74 years old, and 6.1 hours in patients >~ 75 years old. Compared to the consistency of evidence towards longer delay in older patients, the evidence of longer delay in women remain conflicting. Global Registry of Acute Coronary Events [GRACE] [18] including 44,695 patients in 14 countries from 2000 to 2006 found the association between women and longer delay. A large scale registry[23] including 2774

STEMI patients in Germany also found a significant longer delay in women over a 20 years observation time. However, several smaller observational studies failed to achieve the same finding[12,31]. Investigation has been conducted to elucidate the differences between men and women during acute symptom onset comprehensively. Systematic reviews showed that women are more likely than men to report shortness of breath, nausea or vomiting and jaw and neck pain, [32] which has impelled many physicians to believe that women may suffer more “atypical” symptoms of AMI. Moreover, some studies found women were less likely to experience chest pain during symptom onset[33]. However, more recent work failed to find discernible patterns of non-chest pain symptoms in AMI between men and women[34]. Furthermore, the clinical relevance of an AMI without chest pain and its impact on delay time remains questionable [33] and may even be in part due to a reporting bias [35].

2.2.1 Clinical factors

Symptoms of AMI is the first warning signal to trigger patients’ help seeking behavior in the acute phase. However, symptoms varies a lot between patients. Not everyone experienced the typical abrupt heavy chest pain [36] and some of the patients had atypical symptoms such as nausea and fatigue which doesn’t fit the patients’ expectation of an AMI onset. They are unaware that chest pain might occur in the company of other symptoms or that it may not occur at all. [37]

In prodromal phase, von Eisenhart et al[38], found no significant association between prodromal chest pain and prehospital delay during acute phase in a multicenter observational study. Furthermore, Hwang [39] et al found that presence of prodromal symptoms was an independent predictor of delay longer than 3 hours and 12 hours.

In acute phase, continuous symptoms were significantly associated with shorter delay[37]. A sudden onset of the symptoms has been shown in a large scale randomized control trial to be associated with significant shorter delay. However, 65% of the patients in the study experienced slow onset[11 37]. Their finding suggested that current definitions do not reflect the illness scenario experienced by the majority of patients. The typical presentation of AMI from the text book might not be typical at all in reality. Many acute coronary syndrome events start slowly, with mild and intermittent symptoms.

In addition, the results that risk factors of AMI such as hypertension, smoking, obesity etc. are not associated with prehospital delay remain consistent through previous evidences[40].

2.3.1 Situational, appraisal and behavioral factors

The decision to seek medical help for the symptoms of an AMI is made within the complex framework of multiple interrelated variables. In the acute phase, patients' cognitive and behavioral responses are the most direct characteristics affecting the decision delay. How individuals experiencing a heart attack perceive and evaluate their symptoms will directly determine how they behaviorally react to cope with the

symptoms. Based on the previous studies, four major cognitive factors related to delay:

- Risk perception: How patients perceived their risk of AMI?
- Symptom expectation: How much did the patients' actual symptoms fit their expectation of an AMI onset?
- Symptom appraisal: How much did the patients realized the seriousness of their symptoms?
- Symptom attribution: What would the patients attribute their symptom to? To heart? Or other diseases?

Among them, symptom attribution has been reported to be the strongest predictive factor in prehospital delay[41,42]. Dracup [41] et al, reported in 273 AMI patients included in a thrombolytic clinical trial that patients who correctly attribute their symptom to heart disease had a significant shorter delay than those who did not. However, only 33% of the patients initially attribute their symptoms to heart. Atypical symptoms such as nausea, heart burn would mislead the patients to interpret their symptom as gastrointestinal, irrespective of whether they had a previous history of heart disease or not. This finding deliver an important message in terms of how individuals experiencing a heart attack perceive and evaluate their symptoms. A mismatch between patients' expectation of AMI and their actual symptoms (symptom incongruence) is one of the major reason for the misinterpretation of the symptoms.

In addition, studies [43] have shown that the symptom incongruence is associated with less emotional arousal which might lead to the inadequate help seeking behavior.

Patients with atypical and progressive developed symptom not only failed to correctly attribute their symptoms but also underestimate the seriousness of their symptoms and that they needed emergent care. These patients appraised their symptoms as not serous or urgent and waited for the symptoms to subside[11,42]. They thought that the weakness or dizziness they experienced were a natural consequence of the aging process or progressing symptoms of their comorbid chronic diseases. The presence of comorbid conditions may make it difficult for older adults to distinguish symptoms of cardiac origin from those of other chronic illnesses. Furthermore, despite the existing cardiac risk factors, patients has been shown holding an optimistic perception of their risk of having AMI. A national telephone survey[44] revealed that a risk denial is quite widespread among smokers and does not simply reflect a lack of knowledge about health risks related to tobacco. A qualitative study also mention that the diabetic patients thought there is no direct relationship of DM or cholesterol to the development of AMI[45]. A cross-sectional study[46] focusing on the risk perception of cardiac patients also shows that patients tended to underestimate their risk although they had on average two modifiable risks and were highly aware of AMI risk factors. Awareness of cardiac risk factors was weakly correlated with perceived vulnerability for AMI and the quantitative analysis shows a weak relationship between an increased number of the modifiable risks and risk perception.

Due to the misinterpretation of patients' symptom and inaccurate perception of their acute situation, mass media campaign and large scale clinical intervention has been focused on enhancing the knowledge of the patients in order to build up the rational

reaction of the patients. However, as has been mentioned in the last chapter [47], intervention targeting knowledge largely failed to change patients' help seeking behavior. In a more recent multicenter cross sectional study, Albarqouni et al.[48] comprehensively investigate the relationship between knowledge and prehospital delay and did find a beneficial impact of better knowledge. Furthermore, they identified the beneficial impact is due to the adequate knowledge of atypical symptoms, which reinforce the notion that they typical symptoms might actually not be typical enough for the patients to correctly interpret their symptoms.

2.4.1 Psychological factors

Although objective factors such as social demographic or clinical ones have been identified by the prior studies to have certain impact on prehospital delay, none of them can explain majority of the effect. Since patients' subjective perception and cognitive response were proved to play a more important role in affecting the help seeking behavior, the emotional arousal at the acute phase and patients' psychological coping mechanism start to receive increasing attention since 90s[49]. Fear of death, anxiety, denial, personality and health locus of control have been shown to be associated with delay time.

2.4.2 Fear of death

Among them, fear of death has been consistently reported to be associated with shorter delay during AMI onset[50] [51] . Fear of death was interpreted as the emotional consequential reaction of the symptom appraisal of seriousness, which is the direct

drive of initiating help seeking behavior. Albarqouni [52] et al. revealed that the patients experienced fear of death were more likely to experience prodromal symptoms and more often consulted their cardiologists. Therefore, it is not unexpected that patients with fear of death are more alert to their health conditions.

2.4.3 Anxiety

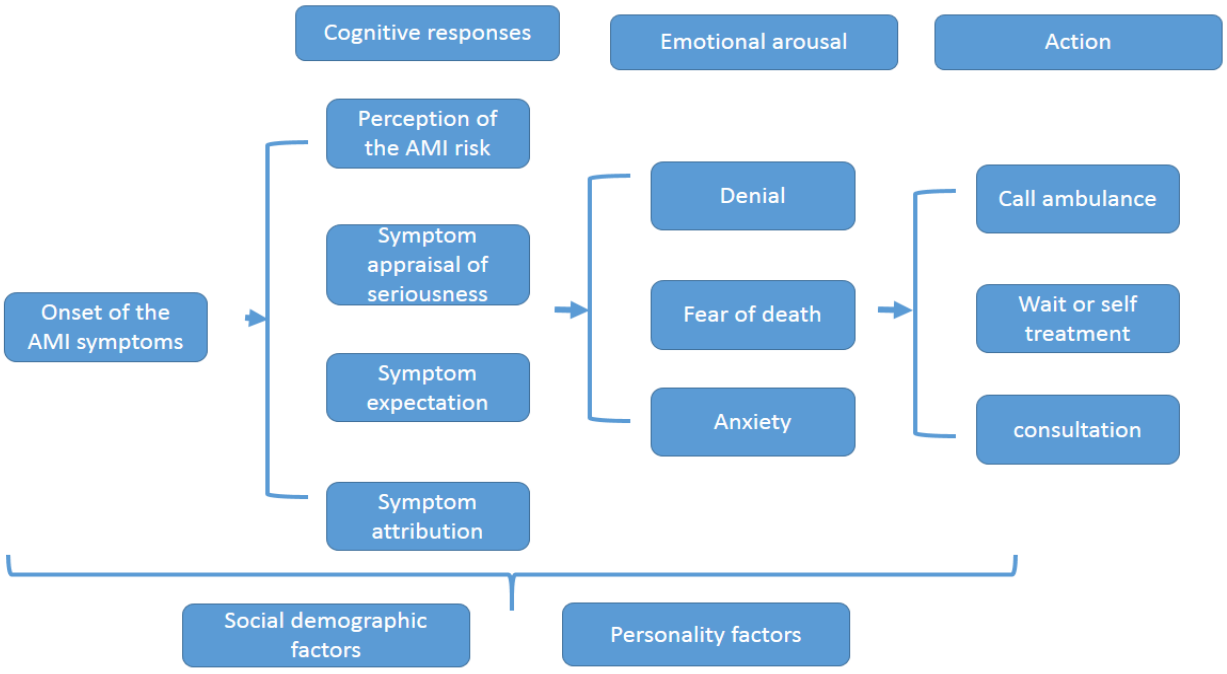
Compare to fear of death, anxiety is a similar but broader concept. Anxiety is a form of negative emotions closely related to fear and is defined as unspecific fear with no clear focus[53]. Whereas fear motivates an individual to engage in defensive behaviors, anxiety is associated with preventive behaviors. Moreover, anxiety can be further divided into state anxiety or trait anxiety which indicating the anxiety induced temporarily by situations perceived as dangerous or anxiety across typical situations that everyone experiences on a daily basis. O'Carroll [54] et al assess the impact of state anxiety on prehospital delay in an exploratory study but failed to find a significant association between state anxiety and delay time. Whereas Moser et al [55] reported that being anxious about the acute symptoms was associated with shorter delay in seeking medical attention. However, evidence regarding the impact of trait anxiety or chronic anxiety is limited.

2.4.4 Denial

Denial has been long emphasized as a major psychological reason causing delay seeking help. It is defined as a coping mechanism towards an unacceptable threatening and a potentially harmful condition by refusing to perceive or consciously acknowledge the impact of a given threat[56]. Under the circumstances of AMI onset,

denial or ‘defensive bias’ is indicating that the patients minimized the seriousness of symptoms which was negatively correlated with the intensity of fear, making seeking treatment less urgent. However, evidences indicating denial associated with longer delay remain equivocal. There were only three small exploratory studies, mainly performed over 10 years ago. Two of them provided a preliminary evidence that denial contributes to delayed seeking treatment with a borderline significance [54] [57] while the other reported no association between denial and delay time.[42] Two methodological problems make it difficult to investigate the role of denial in delay time accurately. The first is that all data related to the patient's decision process had to be collected retrospectively. Since denial is a transitory coping mechanism, it would be difficult to assess denial after the fact. When asking patients’ symptom appraisal of seriousness or symptom attribution, it is impossible to evaluate the degree to which the patients to ward off anxiety. The second difficulty is the lack of an appropriate psychometric instrument. Gentry and Haney[58] used a measure of denial defined as the difference between current self-reported health status and reported health status in the week before infarction. A potential confounding factor in this case is if the patient had been in poor health condition for a long time. Other investigators[59,60] who have assessed denial have indicated that it does not contribute significantly to delay. Therefore, there are quite a few study addressed the relationship between denial and delay base on the indirect assessment such as lower symptom appraisal or emotional awareness[41,49] instead of directly using denial instrument.

Figure 1. Summarizes the concepts under evaluation in this thesis in the form of an acyclic graph, illustrating the behavior model of the patients' decision making during the acute situation.



Chapter 3 Rational and methods

The multicentre, cross-sectional MEDEA study (*Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction*) was conceived with the aim to document the prehospital delay of patients with STEMI, and the factors which may contribute to prolonged delay.

3.1.1 Study design

The patients were recruited from eight different university or municipal hospitals with coronary care units, belonging to the Munich emergency system network clinics. The MEDEA study was approved by the Ethic Commission of the Faculty of Medicine of the Technische Universität München (TUM) on 10.12.2007 and the consent of the Munich Institut für klinische Forschung (IKF) for the participating four municipal hospitals (9.4.2008). The main inclusion criterion was diagnosis of STEMI as evidenced by typical clinical symptoms, ECG changes and myocardial biomarkers levels. Exclusion criteria were: In-hospital STEMI, resuscitation at AMI-onset and language barriers or cognitive impairment impeding patients to answer the questionnaires properly. There were no age restrictions. Standardized operation procedures (SOPs) were implemented to ensure the consecutive referral of eligible patients into the study. To assure a consecutive inclusion into the study, a trained team of physicians screened incoming patients every day of the week and informed

the MEDEA personnel to come to the ward for data collection. All eligible patients were asked for their permission to be interviewed and were required to sign a declaration of consent. Study participation was voluntary, patients were informed about the procedures of the study and they were assured that refusal would not affect their treatment.

3.2.1 Sample

From 12.12.2007 until 31.05.2012, data on 619 patients who were capable of taking part in the study were collected. There were few dropouts in the study since physicians did not inform MEDEA study personnel of AMI patients who were unable to answer the study questionnaire due to their critical condition (e.g. coma). Approximately 18% of patients were excluded: 4% due to not meeting inclusion criteria and 14% due to absence of consent or missing data. Comparison of included and excluded patients showed no significant differences in age, sex, sociodemographic, clinical and other relevant covariates. However, included patient were more likely to have a high-education level and being employed.

3.2.2 Data collection

The data collection process was divided into three sections. Firstly, a bedside interview was conducted with trained personnel within 24 hours after referral from intensive care. Secondly, a self-administered questionnaire was completed by the patient in a calm and non-supervised environment. Thirdly, somatic risk factors were derived from the medical records and assessed by the medical personal of the cardiology departments.

3.3.1 Measures

3.3.2 Pre-hospital Delay (PHD)

Prehospital delay time was the primary outcome defined as the time interval between symptom onset and arrival at the hospital door, measured in minutes. The onset time was triangulated by trained personnel in the interview, using routine events in the patient's life to enable them to set the onset symptoms into a temporal context. This technique has previously been developed and tested by Moser et al., who found that this technique enabled patients who initially did not remember onset-time to successfully recall it[55].Symptom-onset was clearly defined as symptoms that worsened or stayed continuous but did not decrease over time. Nevertheless, defining symptom-onset remained a challenge (for example, patients often had difficulties to differentiate between prodromal symptoms and intermitting acute onset). Arrival at hospital was measured using the time of first ECG in the hospital which has been deeply discussed within the study board as the most accurate and consistent record of arrival across hospitals. The time difference between symptom-onset and first ECG in the hospital constitutes "prehospital delay" (PHD), measured in minutes. PHD time in min was heavily left-skewed and did not approximate a normal-distribution after transformations. Following recent guideline recommendations[1], we dichotomized PHD time into 2 groups (<120, and ≥120 minutes.)

3.3.3 Strcutualed interview: baseline, clinical and behavioural measures

At bedside, comprehensive data on sociodemographic and health related behaviors were assessed, (physical activity, burden of work, smoking).

Health attitudes (perceived AMI-risk, importance attributed to AMI, disapproval of the medical system) and frequency of doctor consultation prior to AMI helped to portray patient's overall approach to health.

Angina pectoris prior to AMI was assessed following the Rose Angina Questionnaire [61]which allowed evaluating: any prodromal chest pain (PCP), Chest pain of unknown origin (unexplained PCP), possible angina and definite angina.

Information on previous doctor consultations: General physicians, cardiologists and no medical contact were assessed by the self-administered questionnaires included in the interview. Information regarding visiting pattern was further differentiated as being acute or routine visits. In case the patients had visited both GP and cardiologist, they were classified into cardiologist treatment group.

The Response of Symptoms Questionnaire[62] was used to obtain information factors contributing to delay in the following domains: (1) the context in which MI symptoms appeared (at home, during work etc.); (2) to address with whom, and what the patient was doing when the signs and symptoms occurred; (3) responses of witnesses to patient symptoms; (4) behavioral responses to symptoms (e.g. wait and see; trying to relax;, calling the emergency system; (5) cognitive response to symptoms (e.g. symptom appraisal).
Additionally, subjective rating of helplessness, fear of death and fear before seeking help was assessed in one-single items instruments. The reason for seeking help was an open item, and coded into the options: fear, pain, family, peer pressure and others. Regarding the decision to get help, the question was raised whether or not the decision was made by the patient himself or somebody else. Mode of

transportation was coded in the interview as self-transportation, transportation by others and transportation via ambulance.

3.3.4 Information from the self-administered questionnaires

a. AMI-knowledge

Knowledge of AMI symptoms was measured using a modified German version of the ACS Response Index Questionnaire[63], which was reviewed by experienced cardiologists as well as patients' representatives. It is an 18-item instrument including two domains. (1) Knowledge of AMI symptoms subscale: from a list of 13 predefined symptoms (8 were correct and 5 were distractor), patients were asked to correctly identify symptoms that could be a representative of AMI. (2) Knowledge of appropriate behavior subscale: patients were also asked to respond to additional five statements related to the appropriate behavior during AMI. The total knowledge score was 18, and for analysis purposes the score was dichotomized by the median (Low: <14, High: >=14).

b. Psychological characteristics

The self-administered questionnaire contained psychometric instruments measuring various psychological outcomes

Affective disorders

Depression was assessed with the Major Depression Inventory (MDI)[64]—a self-report mood questionnaire able to generate an ICD-10 or DSM-IV diagnosis of clinical depression. The MDI contains 12 items. The DSM-IV define patients with

major depression when they had more than five symptoms in the MDI scale, of which at least one must be a ‘core’ symptom.

Anxiety was assessed with the German version of Generalized Anxiety Disorder scale (GAD-7)[65]. It is composed of 7 items, rated on a four-point Likert scale from not present to very high, leading to an overall score ranging from 0 to 21. A suspected diagnosis of GAD is defined by a GAD-7 score greater than or equal to 10. Using the threshold score of 10, the GAD-7 has a sensitivity of 82% for GAD.

Perceived Stress

Stress was measured by two items, a) the IHS, a 3-item instrument measuring stress in financial, family and work-related context rated on a four-point Likert scale, ranging from 3 (never) to 12 (permanent stress). Feeling irritable, filled with anxiety, or as having sleeping difficulties as a result of conditions at work or at home.

Somatic Symptom disorder

The somatic symptom scale (SSS-8)[66] measures somatic symptom burden, comprising 8 items to detect somatic, anxiety and depression-related symptoms. Its score ranges in between 0-32. Stress was defined as feeling irritable, filled with anxiety, or as having sleeping difficulties as a result of conditions at work or at home.

Personality concepts

Type-D personality was measured using the Type-D Scale 14 (DS-14) which is divided into two subscales with each 7 items, measuring social inhibition and negative affectivity[67].

c. Mediators of patient perception

Resilience

Resilience was measured in a short 5-items version (RS-5) developed from original version of the RS-14[68]. This tool measures the domains of personal competence and acceptance of self and life, ranging from a score of 0-28.

Cardiac denial

Denial regarding cardiac illness was measured in the 8-item Cardiac Denial of Impact Score (CDIS)[69], which originated from the earlier work of Hackett [56] and Cassem. The CDIS is composed of 8 items, rated on a 5-point Likert scale from not present to very high, allowing the overall score to range from 8 to 40. The test-retest reliability, construct and discriminant validity have been reported by the developers as sufficient.

To define an index study population of deniers, we followed the procedure of earlier investigations which applied the median split as a cutoff point [54,57], leading to a denial (>24) and non-denial (≤24) group.

Locus of control

Health locus of control was assessed MHLC-Scales[70] in the German version [71] [72].Following Marshall [73], this differentiates the degree to which people believe that their health is caused by internal factors (6 items), and perceived external causation into 'powerful others' and 'chance' (three items each). According to Marshall[73], internal factor was found split into 'self-blame' and 'self-response'. Each item is assigned an agreement score that ranges from 1 (strongly disagree) to 5 (strongly agree). Example items are "The main thing which affects my health is what I myself do", "Whatever goes wrong with my health is my fault", "Having regular contact with

my physician is the best way for me to avoid illness", and "My good health is largely a matter of good fortune". For each subscale, a sum-score is constructed, with higher values indicating stronger belief. The instrument has been found to be reliable and valid in the above-cited study by Abel et al.

Well-being

Well-being was measured by the WHO-5[74], a 5-items instrument developed by the WHO to measure happiness, energy, motivation and interest in daily life. The score can range from 0 to 100, suboptimal well-being being indicated by a score equal or lower to 50

3.4.1 Data analysis

Differences between dichotomous variableswere assessed using the Chi-square test. When comparing ordinal variables with more than two categories, the Mantel-Haenszel chi-square test was used. Differences in age were assessed using the t-test. The non-parametric Wilcoxon test was used for assessing differences in median prehospital delay times. Pearson correlation was used for assessing the dose-response relationship between denial level and delay time.

Multivariate Logistic regression model was applied to assess the association between GAD and patients' responses to the symptom onset. Due to the fact that anxiety is highly correlated with other psychological factors, we additionally assessed the cumulative effect of stress and exhaustion on patients' responses also using logistic regression model. Furthermore, the association between GAD and the

chance of longer delay were also using logistic regression with different grades of adjustments for psychological factors. Patients who delayed more than two hours are defined as delayed group. Adjustments were made for fear of death, acute anxiety during the symptom onset (model 2), and additionally for stress (model 3), exhaustion (model 4) and depression (model 5).The relative risk for longer delay is presented as odds ratio (OR) with 95% confidence interval (95% CI). Mediation models were calculated in order to assess the intermediate effect of chest pain in the association between old women and prehospital delay. Mediation analyses were conducted in R, using the mediation package which calculated boot-strapped confidence intervals using 1000 simulations in order to increase the power of estimates. All other statistical analyses were run in SAS (Version 9.3, SAS-Institute Inc., Cary, NC, USA). The significance level α was set at .05. The analysis and the description in this paper follow the STROBE guidelines for cross-sectional studies[75].

3.5.1 Aims

This thesis has the following specific aims:

Manuscript 1: Is denial a maladaptive coping mechanism which prolongs pre-hospital delay in patients with ST-segment elevation myocardial infarction?

Using data from MEDEA the aims were:

1) To investigate whether a higher level of denial exert an independent impact on prolonging delay time during ST-segment elevation myocardial infarction

2) To investigate whether denial facilitates a favorable impact on regulating negative affectivity during the acute situation of STEMI onset

Manuscript 2: Impact of generalized anxiety disorder (GAD) on prehospital delay of acute myocardial infarction patients. Findings from the multicenter MEDEA study

Using data from MEDEA the aims were:

3) To investigate the impact of GAD on prehospital delay and delay related cognition and behavior.

4) To investigate the impact of GAD on patients' cognitive and behavioral responses during the AMI symptom onset.

Chapter 4 Summary of the results

In **manuscript 1**, 42% of the AMI patients were defined as deniers. They were more likely to be younger (p=0.034), male (p=0.007), living with someone (p=0.009) and were less likely to suffer from prodromal symptoms (p=0.011). Furthermore, deniers were found suffered less from major depression (p=0.039), anxiety (p=0.011) and suboptimal wellbeing than non-deniers during the final 6 months prior to STEMI (p=0.01). During STEMI, they tended to perceive lower pain strength (p=0.042), less racing heart (p=0.02), less shortness of breath (p=0.028), and also less vomiting (p=0.0142), especially in men. When assessing the association between denial and delay time as the major outcome, we did not find a significant association. However, in a sensitivity analysis, denial accounted for roughly 40 minutes' delay (356 vs. 316.5min p=0.022) in the time window of 3 to 24 hours. To explore the direct effect of denial on patients' cognitive and behavioural responses during the acute situation. We found the deniers tented to have less serious symptom appraisal and more likely to ignore the symptoms and keep on doing what they were doing (p=0.025). I conducted all the data analysis and wrote the whole manuscript.

Manuscript 2 investigated the impact of anxiety on prehospital delay. We identified 71 (11%) of the AMI patients as having generalized anxiety disorder (GAD). Patients with GAD were more likely to be younger (p=0.05) but did not show differences in sex. As expected, GAD were highly correlated with negative affectivity such as stress (p <0.0001), vital exhaustion (p <0.0001), suboptimal well-being (p <0.0001) and depression (p <0.0001). During the acute phase, patients with GAD were more likely to perceive a higher AMI risk and thus leading to a lower chance of delay longer than two hours (OR: 0.58, 95%CI 0.35-0.96). The effects were independent

from the acute anxiety at onset of symptoms and even fear of death and remained significant after stepwise adjustment for stress, exhaustion and depression. I conducted all the data analysis and wrote the whole manuscript.

Chapter 5. Discussion and conclusions

5.1.1. Discussion

Denial and anxiety are two of the most common defense mechanisms among patients facing acute myocardial infarction onset. Denial is one of the most often addressed factors causing delay in the previous literatures. However, comprehensive investigation concerning denial is limited due to the methodological difficulty of assessment. Counterintuitively, our finding revealed a minimal effect of denial on delay. Deniers exhibited a 40 minutes longer delay in the patients delayed within a time window between 3 to 24 hours which only covered 50% of the study population. Although it has been often claimed that denial causes delay of seeking help during AMI [43], there were only three studies mainly conducted ten years ago using the specific denial instruments to assess denial in the investigation of factors associated with delay. O'Carroll [54] et al. (2001) analyzed the impact of psychological factors including denial on delay in 85 AMI patients and found a borderline significant delay time- prolonging effect of denial using a cut-off point of 4h. The replication study of Stenström [76] et al. (2005) including 107 AMI patients and the identical cut-off-point also identified a longer delay time in deniers. Perkins-Porras [57] et al. (2008)

using a more clinical relevant cut-off point (130 minutes) to define delay also demonstrated an significant effect of denial on longer delay time. However, within the 177 patients of the study, patients with NSTEMI and unstable angina were also included. The heterogeneity nature of NSTEMI clinical manifestation would diminish the reliability of the results.

Furthermore, contrary to the assumption that denial will lead to an underestimation of their cardiac risk or less severe symptom appraisal, we did not find any association between denial and patients' cognitive responses to the symptom onset. To the best of our knowledge, the present investigation is the first to directly investigate the association between denial and delay relevant perceptions.

Moreover, our investigation also exhibited a protective impact of denial. During six month prior to AMI, denial was associated with lower levels of depressed mood, anxiety and with a higher level of well-being which coincides with the theoretical assumption that denial may provide psychological protection against negative affectivity[77]. During the acute symptom onset, denial was associated with less pain severity, racing heart and shortness of breath but not with the objective severity of the infarction: no-significant difference concerning length of care, incidence of cardiac arrest, or complications during the post-acute course. As the denial assessment in the current investigation was focusing on a long term trait of the patients, denial here not only provided the patients a better daily mental state but also protected the patients by perceiving less suffering during the acute situation. It has been reported that denial was associated with faster recovery, better psychosocial readjustment and lower mortality[78]. However, more recently, a study including 241 post MI patients in Malaysia shows a higher prevalence of medication

non-adherence in patients with denial of illness[79]. The conflicting evidences of denial might due to the inconsistent assessment. As has been mentioned by Moser [80] et al, Hackett and associates, Gentry and Haney developed the two most frequently applied instruments which define denial as an optimistic assessment of individuals' health status while the denial which most physician assumed was a transitory coping mechanism that is difficult to evaluate after the fact. Further investigation is warranted to assess the denial of patients in a longitudinal approach to help us better understand the psychological process of the decision making during acute situation.

In manuscript 2, we comprehensively evaluated the impact of GAD on prehospital delay in patients facing an AMI and identified a favorable effect of GAD on reducing delay. More important, the beneficial effects of GAD on prehospital delay remain significant even after we controlled for acute fear of death, depression, exhaustion and perceived stress which indicate a powerful and independent protective effect of GAD on prehospital delay. Our finding revealed that the pathological alertness of GAD might actually be protective under certain circumstances. Different from acute anxiety, major characteristics of GAD is excessive anxiety and worry that he or she finds difficult to control about a number of events or activities longer than six months. During the six month prior to AMI onset, GAD might play as a "driver" for individuals to address their health needs more regularly and conscientiously and seek help at the early signs of the disease. Dubayova [53]et al. reported in a systemic review including 15 studies that anxiety has a significant positive effect of prompting patients' help seeking behavior. Moser et al[55] also reported that a higher level of anxiety about the symptoms would lead to less delay of seeking medical attention. Parker [81]et al investigated the impact of GAD on 489 AMI patients' five year survival

and found that GAD patients received more medical tests and tended to take part more often in post- AMI rehabilitation programs. However, all the other subtypes of anxiety pointed to a poorer cardiac outcome. More recently, Meyer et al [82] reported in a cohort study including 470 patients referred for PCI that anxiety is associated with a reduction in both mortality and major cardiac events with a five years follow up. However, O'Carroll [54] et al. failed to find an association between state anxiety and delay shorter than four hours. Qualitative studies[41,83] revealed that the worry of troubling others or the financial consequence of seeking help would cause delay while the worry of their symptoms would urge the patients to seek help. In addition, GAD patients did not experience a different pattern of acute symptoms compared to non-GAD patients which indicated the reason of faster help seeking behavior of GAD patients might not because of more severe symptoms.

Our finding showing that GAD patients had a higher self-perceived MI risk than non-GAD patients might partially explained the reason of a shorter delay in GAD patients and higher MI risk perception has been well established factors leading to a faster help seeking behavior. Furthermore, our study reveals the association of GAD patients with a better prognosis in the post-acute phase of AMI. Based on the highly time dependent nature of thrombolysis treatment [84], this is probably a consequence of a shorter delay time of GAD patients. However, if the GAD patients further suffered from excess stress or exhaustion, the protective effect would no longer be significant anymore.

Although the study identified a prominent favorable effects in patients meeting GAD criteria through the acute course of AMI, GAD as an established mental health disorder, not surprisingly, was associated with more negative emotions (depression,

exhaustion and perceived stress and thus impaired psychological well-being) as its disease burden for the patients during the prodromal stage. This is in line with the observation shows that GAD are frequently comorbid with depression [85,86]

Taken together, GAD has been found to be a protective factor for patients facing AMI onset by prompting a faster help seeking behavior. However, the adequate coping during acute situation was accompanied with more suffering from long term negative emotions. Moreover, anxiety has been often reported as trigger for cardiac diseases such as ventricular tachycardia and ventricular fibrillation [87]. Moser et al. [87]reported in a large cohort including 3522 patients with coronary heart diseases that higher level of anxiety was associated with greater risk of recurrent ischemia, reinfarction and increased mortality. Follow up study is warranted to investigate the long term effect of GAD on the prognosis of AMI patients.

5.1.2. Conclusion

In conclusion, this doctoral thesis has investigated the two most important psychological factors for prehospital delay. Counterintuitively, our findings showed the protective effect of two factors which were considered as maladaptive coping mechanism during this acute situation. Denial and anxiety worked complimentary in patients facing live threatening situation to help them find a balance between adequate behavior and proper mood regulation. Our finding provided the evidences for the healthcare providers to utilize the patients' emotional responses to achieve a better effect of intervention to reduce delay.

5.2.1. Future perspective

The next analysis awaiting peer review aims to investigate the impact of physician consultation during the six month prior to AMI onset on prehospital delay. Delay time was compared between patients with cardiologists' surveillance, patients with general physicians' surveillance and patients with no medical contact by using nonparametric Wilcoxon test. Mediation analyses were calculated to evaluate the consequences of cardiologist consultations on the interpretations of symptoms. The study aims to find a better timing for a more effective intervene to reduce delay. These results should reveal whether clinical consultation is a better timing for patients with high AMI risk to receive more specific intervention to reduce delay at the upcoming adverse cardiac event.

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Chapter 6. Is denial a maladaptive coping mechanism which prolongs pre-hospital delay in patients with ST-segment elevation myocardial infarction?

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Is denial a maladaptive coping mechanism which prolongs pre-hospital delay in patients with ST-segment elevation myocardial infarction?

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ABSTRACT

Objective: During an acute myocardial infarction, patients often use denial as a coping mechanism which may provide positive mood regulating effects but may also prolong prehospital delay time (PHD). However, empirical evidences are still sparse.
Methods: This cross-sectional study included 533 ST-elevated myocardial infarction (STEMI) patients from the Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction (MEDEA) study. Data on sociodemographic, clinical and psycho-behavioral characteristics were collected at bedside. The outcome was assessed using the Cardiac Denial of Impact Scale (CDIS) with the median split as cutoff point. A total of 206 (41.8%) STEMI patients were thus classified as deniers.
Results: Deniers were less likely to suffer from major depression ($p = 0.04$), anxiety ($p = 0.01$) and suboptimal well-being ($p = 0.01$) compared to non-deniers during the last six months prior to STEMI. During STEMI, they were less likely to perceive severe pain strength ($p = 0.04$) and racing heart ($p = 0.02$). Male deniers were also less likely to perceive shortness of breath ($p = 0.03$) and vomiting ($p = 0.01$). Denial was not associated with overall delay time. However, in the time window of 3 to 24 h, denial accounted for roughly 40 min extra delay (356 vs. 316.5 min $p = 0.02$ $n = 196$).
Conclusions: Denial not only contributes to less suffering from acute heart related symptoms and negative affectivity but also leads to a clinically significant delay in the prevalent group.

1. Introduction

Denial has been commonly framed as a psychological mechanism for "ego defense" [1] which individuals unconsciously employ as reaction to the confrontation with an unacceptable threatening and a potentially harmful condition by refusing to perceive or consciously acknowledge the impact of a given threat. In the early decades of psychological theory building, denial was regarded as "immature" [1,2] mainly because subjects with high levels of denial may act maladaptive: rejecting or distorting reality in order to defend against unacceptable impulses. More recently, however, positive aspects of denial as a coping mechanism have been acknowledged by highlighting the provision of psychological protection against the perception and processing of subjectively painful or distressing information [3]. Here, denial may facilitate positive mood regulating effects when facing traumatic events and may enhance resilience in these subjects.

An acute myocardial infarction (AMI) with its traumatizing and life threatening onset [4] may qualify as a condition where denial may serve as a prominent maladaptive coping mechanism [4–6]. Indeed, some small exploratory studies, mainly performed over 10 years ago, provided a preliminary evidence that denial contributes to delayed adherence to effective cardiac treatment by disavowing of the diagnosis and by minimizing the perceived symptom burden and symptom severity [7–9]. However, it is not unlikely that denial also exerts positive effects during the acute stress situation of an AMI. Indeed, one recent study has demonstrated that denial can also help patients to go through stressful somatic disease treatment conditions and react better to the medical treatment [10].

The suspicion that denial may act on the patient's decision to seek adequate help after the onset of an ST-segment-elevation myocardial infarction (STEMI) is of a particular concern because patient's delay in presenting to the hospital promptly after STEMI onset is a major factor limiting the potential of acute reperfusion to further reduce cardiovascular mortality [6]. Denial has the potential to play an important role

Abbreviations: AMI, acute myocardial infarction; STEMI, ST segment elevation myocardial infarction; PHD, Prehospital delay; MEDEA, Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction.

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in this context. Given the limited evidence on this topic, we aimed to investigate whether a high level of denial exert an independent impact on prolonged delay time during STEMI. Furthermore, we investigate whether denial facilitates a favorable impact on mood regulating conditions (depression, anxiety) and the perceived severity of the STEMI.

2. Methods

The multicenter, retrospective cross-sectional MEDEA study (Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction) was conceived with the aim to evaluate prehospital delay of STEMI patients, and the factors which may contribute to prolonged delay.

2.1. Study design

The patients were recruited from the university or municipal hospitals, which have a coronary care unit and belong to the Munich emergency system network hospitals (see the acknowledgement). The main inclusion criterion was the diagnosis of STEMI as evidenced by typical clinical symptoms including: chest pain/discomfort lasting for 10–20 min or more (not responding fully to nitroglycerine), radiation of the pain to the neck, lower jaw, or left arm, dyspnea, or syncope [11]; ECG changes and myocardial biomarkers levels [12]. Patients were excluded from the study if they had to be resuscitated, if AMI occurred while already hospitalized and if they were unable to answer the questionnaires properly due to language barriers or cognitive impairment. There were no age restrictions.

Standardized operation procedures (SOPs) were implemented to ensure the consecutive referral of eligible patients into the study.

All patients were informed of the aim and procedures of the study and also that taking part in the study would have no effect on their treatment. All participating patients were required to sign a declaration of consent. Physicians updated MEDEA personnel twice a week on eligible patients. Bed-side interviews were conducted in the hospital ward within 24 h after referral from intensive care.

2.2. Sample

From 12.12.2007 until 31.05.2012, a total of 755 patients were screened for eligibility. In 619 patients, a diagnosis of STEMI was confirmed. As can be seen in Fig. 1, approximately 18% of patients were excluded: 4% due to not meeting inclusion criteria and 14% due to absence of consent. From the 619 eligible patients, a total of 86 patients were excluded because of missing data in the Cardiac Denial of Impact Scale (CDIS). A drop-out analysis was conducted to compare the baseline information between the patients with ($n = 533$) and without ($n = 86$) valid CDIS data. This analysis demonstrated that the CDIS responders were significantly younger ($M_{res} = 61.63$, $M_{non\text{-}res} = 66.53$, $p = 0.001$), better-educated {$N_{res} = 208$ (39.02%), $N_{non\text{-}res} = 48$ (55.81%), $p = 0.003$} and more likely to be employed {$N_{res} = 278$ (52.16%), $N_{non\text{-}res} = 26$ (30.23%), $p = 0.0002$}. No differences in living situation (living alone or not) ($p = 0.15$) and sex ($p = 0.15$) were found between responders and non-responders.

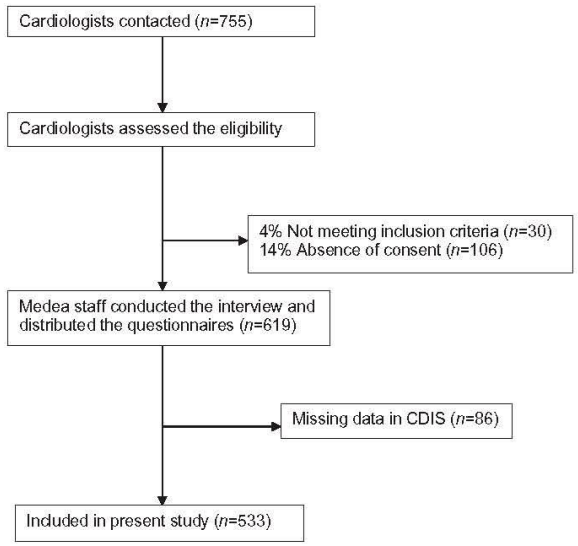

Fig. 1. Consort chart of patients in MEDEA.

2.3. Data collection

The data collection process was divided into three sections. Firstly, a structured bedside interview was conducted with trained personnel. Secondly, a self-administered questionnaire was filled by the patient without supervision. Thirdly, data were collected from the hospitals' patient charts.

The hospital patient charts and bedside interviews provided data on demographic information, like age, sex, living situation (living alone or not), risk factors, presenting symptoms, important clinical measures as well as possible complications. Prodromal symptoms were defined by the presence of any symptom related to coronary artery disease within the last six months prior to STEMI, including prodromal chest pain, dyspnea, sweating, palpitation, faint, sleep disturbance and fatigue.

2.4. Measures

2.4.1. Prehospital delay (PHD)

Patients were asked to recall at what time acute symptoms began. The time difference between symptom onset and first ECG at hospital entry constitutes "prehospital delay" (PHD), measured in minutes. PHD was thus available as a continuous variable which was heavily left-skewed and did not approximate a normal distribution after log-transformations.

2.4.2. Cardiac Denial of Impact Scale (CDIS)

Denial was assessed with the CDIS [13], which originated from the earlier work of Hackett and Cassem [14]. The CDIS is composed of 8 items, rated on a 5-point Likert scale from not present to very high, leading to an overall score ranging from 8 to 40. The test-retest reliability, construct and discriminant validity have been reported by the developers [13] as sufficient.

To define an index study population of deniers, we followed the procedure of earlier investigations which applied the median split as a cut-off point [7,9], leading to a denial (>24) and non-denial (≤24) group. Interestingly, this particular cut off point was identical with the two other studies under consideration [7,9], indicating that the scale is stable across diverse study population.

2.4.3. Psychological measures

Anxiety was assessed with the German version of Generalized Anxiety Disorder scale (GAD-7). It is composed of 7 items, rated on a on a 5-point Likert scale from not present to very high, leading to an overall score ranging from 7 to 35. A GAD-7 score greater than or equal to 10 indicates anxious participants [15].

Depression was assessed with the Major Depression Inventory (MDI) - a self-report mood questionnaire able to generate an ICD-10 or DSM-IV diagnosis of clinical depression. The MDI contains 12 items. According to the DSM-IV definition, patients who had at least five symptoms in the MDI scale, of which at least one must be a 'core' symptom, were diagnosed with major depression [16].

Well-being was evaluated through the WHO-Five Well-Being index. It contains five items on a 6-point scale that range from 0 to 25. Thereafter, the raw scores are transformed into a scale that range from 0 to 100 [17]. WHO-5 score less than or equal to 50 indicates suboptimal well-being [18]. Effectiveness of the index has been supported in evaluation of emotional well-being in patients with cardiovascular diseases.

Type D personality was assessed by DS14 with two subscales containing one assessing negative affectivity and the other assessing social inhibition. Both scales included 7 items ranging from 0 (false) to 4 (true) [19]. Type D personality was identified if both subscales scored ≥10 points [20].

2.4.4. Patient behavioral responses to STEMI

The structured bedside interview also includes a German version of the Response to Symptoms Questionnaire [21], which assesses the behavior and subsequent reactions of both the patient as well as witnesses in the following areas: social context in which symptoms occurred and bystanders responses, behavioral responses to the symptoms, cognitive responses to the symptoms and emotional responses to the symptoms. The instrument also includes one item on symptom expectation, which measures the congruence between symptom expectation and perception (11 items, 5 point Likert scale, >3 rated was used as cut-off to define a high level).

2.5. Data analysis

Differences between dichotomous variables were assessed using the Chi-square test. When comparing ordinal variables with more than two outcomes, the Mantel–Haenszel Chi-square test was used. Differences in age were assessed using the *t*-test. The non-parametric Wilcoxon test was used for assessing differences in median prehospital delay times. Pearson correlation was used for assessing the dose-response relationship between denial level and delay time. A total of 22 patients were excluded from the multivariate analysis due to missing values in covariates. No significant differences were found between the included and the excluded patients.

All statistical analyses were run in SAS (Version 9.2, SAS-Institute Inc., Cary, NC, USA). The significance level was set at $p < 0.05$. The analysis and description in this paper follow the STROBE guidelines for cross-sectional studies [22].

3. Results

A total of 533 patients were included in the present study with 134 (25.14%) women and 372 (69.79%) men aged between 30 and 93 years (mean age 61.68 years SD = 12.20). In the total sample, the median delay was 203 (101.5–695.0) minutes.

3.1. Prevalence and distribution of denial in patients with STEMI

The CDIS score was normally distributed with a mean of 23.61 ± 5.16 and a median of 24 leading to a total of 224 (42.03%) patients as denier (CDIS ≥ 24). As shown in Table 1, patients with higher levels of denial were more likely to be younger ($p = 0.03$, 60.52 ± 12.07 vs. 62.77 ± 12.11), male ($p = 0.01$), living with someone ($p = 0.01$) and were less likely to suffer from prodromal symptoms ($p = 0.01$). Furthermore, patients with higher levels of denial were less likely to suffer from depressive mood ($p = 0.04$), anxiety ($p = 0.01$) and suboptimal well-being in the six months prior to STEMI ($p = 0.01$).

As also can be seen in Table 1, there were no significant differences between patients with a high level of denial and those with a low level of denial regarding educational levels, employment status and the presence of cardiac risk factors. Furthermore, when considering the medical history of the post-acute infarction phase (intensive care, complications and cardiac arrest), we also did not observe any significant differences in denial levels, suggesting that the severity of the infarction had no significant association with denial.

Table 1
Sociodemographic and clinical characteristics of the study population stratified by denial ($n = 224$) and non-denial ($n = 309$) and by sex.

	Cardiac Denial of Impact Scale ($n = 533$)				*p* Value	
	Missing	Denial	Non-denial	Overall	Women	Men
Socio-demographic factors						
Sex (female)	–	43 (32.09)	91 (67.91)	**0.01**		
Sex (male)	–	181 (45.36)	218 (54.64)			
Living alone	–	50 (22.32)	101 (32.69)	**0.01**	0.38	**0.04**
Employed	–	126 (56.25)	141 (49.19)	0.11	0.28	0.07
Education (secondary school and above)	–	82 (36.61)	126 (40.78)	0.33	0.07	0.93
Psychological factors						
Depressed mood	10	94 (41.96)	164 (53.07)	**0.04**	0.16	**0.05**
GAD (score > 10)	0	20 (8.93)	51 (16.50)	**0.01**	**0.04**	0.07
Suboptimal well-being (score < 50)	–	51 (22.77)	93 (33.01)	**0.01**	0.31	**0.02**
Somatic risk factors						
Hypertension	5	128 (57.40)	190 (62.30)	0.26	0.30	0.50
Hypercholesterolemia	5	73 (32.88)	122 (39.87)	0.10	0.86	**0.04**
Diabetes mellitus	6	47 (21.36)	55 (17.92)	0.32	0.88	0.28
Smoking	1	129 (57.59)	183 (59.42)	0.67	0.74	0.44
Obesity	5	78 (35.14)	91 (29.74)	0.41	0.09	**0.02**
Family history of MI	2	107 (47.98)	155 (50.32)	0.59	0.76	0.69
Medical history						
Prodromal symptoms[a]	–	135 (60.27)	219 (70.87)	**0.01**	0.25	**0.03**
Stent history	4	14 (6.31)	27 (8.79)	0.29	0.51	0.35
MI history	–	21 (9.38)	43 (13.92)	0.11	0.46	**0.02**
Post-acute course						
Intensive care ≥3 days	5	152 (68.47)	199 (65.03)	0.41	0.96	0.34
Any complications	–	40 (17.86)	56 (18.12)	0.94	0.16	0.40
Cardiac arrest	–	11 (4.91)	10 (3.24)	0.33	0.76	0.26

Values are *n* (%). Bold means significant *p* values at <0.05 level. Abbreviations: MI = myocardial infarction; GAD = generalized anxiety disorder.
[a] Prodromal symptoms include: prodromal chest pain, dyspnea, sweating, palpitation, faint, sleep disturbance and fatigue.

3.2. The association between denial and patients' cardiac symptom perception and behavior responses during STEMI

In the face of acute STEMI, deniers tended to perceive lower pain strength ($p = 0.04$), less racing heart ($p = 0.02$) and were less likely to recognize the symptoms as signs of MI ($p = 0.01$), as can be seen in Table 2. Men but not women with high levels of denial reported less shortness of breath ($p = 0.03$), vomiting ($p = 0.01$) and perceived their cardiac risk as less serious ($p = 0.05$). Female deniers tended to attribute their symptoms less often to their heart ($p = 0.03$).

As can be seen in Table 2, we observed only minimal differences between deniers and non-deniers concerning their behavioral reactions to symptom onset. However, deniers were more likely to keep on doing ongoing activities ($p = 0.03$), but tended to alarm the emergency system more often ($p = 0.09$). Female deniers were more likely be driven by others ($p = 0.05$) compared to driving on their own ($p = 0.03$).

3.3. The impact of denial on prehospital delay

As can be seen in Table 3, the median overall delay time in deniers was 216 min and in non-deniers 200 min, not reaching a significant difference. When we stratified the data, we found no significant difference in either sex groups.

Fig. 2, displaying the cumulative frequency curve of the prehospital delay of deniers and non-deniers, shows an overall discrete distribution of two groups, proving a slight yet nevertheless non-significant difference from deniers. However, inspection of the figure disclosed a significant 40 min extra delay (356 vs. 316 min) in denial group in the time window ranging from 3 to 24 h.

Correlation analysis between increasing levels of delay and increasing delay time disclosed a dose-response relationship ($r = 0.16$ $p = 0.02$) (see Appendix A).

In sensitivity analysis, we additionally investigated differences in symptom perception in three time windows of delay: delay <3 h, delay 3–24 h and delay >24 h. As can be seen in Table 4, we observed dose-response relationships between delay time and symptom perception; with increasing delay time, perception of typical symptoms (shortness of breath, sweating, chest pain, vomiting) ($p = 0.02$) and symptom severity ($p = 0.0001$) decreased. In the most favorable time window of <3 h, deniers and non-deniers exhibited no significant differences in perceived symptom burden (23.27 vs. 23.66 $p = 0.58$) or symptom severity (23.40 vs. 23.59 $p = 0.79$).

4. Discussion

4.1. The impact of denial on delay time

Denial is a concept often encountered to describe a psychological mechanism of defense which serves to provide protection against perception and processing of subjective traumatizing or painful properties of a given event [3] [5]. On one hand, given the possible traumatizing consequences of AMI, denial might be favorable on the occasion, on the other hand, in patients who employ denial as their dominant means of coping with distressing events, they could be assumed to ignore reality and delay acute coronary care when facing with STEMI. However, the first major finding of this investigation in a sample of 533 STEMI patients showed that patients characterized as deniers exhibited only minimally longer overall delay times to reach the coronary care unit of a hospital compared to non-deniers (216 vs. 200 min). This time difference did not reach significance.

On a first view, this finding seems to be surprising not only because of the theoretical framework of denial as a psychological mechanism to disavow clinical realities but also because preliminary evidence suggests a significant impact of denial on a prolonged delay time. To the best of our knowledge, only 3 studies with small sample sizes have investigated this topic so far: O'Carroll et al. (2001) analyzed the impact of denial on delay in 85 AMI patients and demonstrated that denial had a significant (however clinically small) effect on delay (with a cut-off point of 4 h) [7]. The replication study of Stenström et al. (2005) with 107 AMI patients and the identical cut-off-point confirmed a longer delay time in deniers [8]. Perkins-Porras et al. (2008) with a more meaningful cut-off point of 130 min were the first to

Table 2
Patients' responses and behavioral patterns in the study population, stratified by denial ($n = 224$) and non-denial ($n = 309$) and by sex.

	Patients responses and behavior patterns				*p* Value	
	Missing	Denial	Non-denial	Overall	Women	Men
Presenting symptoms						
Chest pain	–	201 (89.73)	273 (88.35)	0.21	0.76	0.57
Sweating	–	124 (55.36)	188 (60.84)	0.08	0.16	0.37
Shortness of breath	–	63 (28.13)	111 (35.92)	0.06	0.42	**0.03**
Vomiting	–	23 (10.27)	47 (15.21)	0.10	0.76	**0.05**
Exhaustion	–	33 (14.73)	42 (13.59)	0.71	0.08	0.59
Racing heart	–	13 (5.80)	33 (10.68)	**0.05**	0.83	**0.05**
Typical symptoms (>2)	–	53 (23.66)	91 (29.45)	0.14	0.39	0.28
Evaluation of symptoms						
Pain strength (score ≥ 8)	8	102 (46.58)	170 (55.56)	**0.04**	0.07	0.25
Low symptom severity (yes vs. no)	3	124 (64.50)	185 (55.70)	0.06	0.13	0.17
Low risk perception (high vs. low)	26	192 (89.72)	249 (84.98)	0.12	0.21	**0.01**
Symptom recognition as MI (high vs. low)	7	90 (40.54)	156 (51.32)	**0.01**	0.42	**0.01**
Attribution to the heart	4	127 (57.47)	155 (50.32)	0.10	**0.03**	0.40
Patients' reactions to the symptom onset						
Waiting for the symptoms to resolve	1	142 (63.39)	190 (61.69)	0.69	0.94	0.62
continuing doing ongoing activities	1	54 (26.20)	53 (18.50)	**0.03**	0.17	0.09
Trying to relax	2	84 (37.67)	128 (41.60)	0.37	0.86	0.36
Calling someone for help	1	14 (6.25)	19 (6.17)	0.97	0.87	0.81
Calling a general physician	–	19 (8.48)	32 (10.39)	0.46	0.78	0.33
Dispatching the emergency system	1	91 (40.63)	107 (34.74)	0.17	0.09	0.49
Transportation to the hospital						
Via ambulance	–	92 (41.26)	122 (36.91)	0.70	0.42	0.50
Via other drivers	–	14 (6.25)	11 (3.56)	0.17	**0.05**	0.52
Self-driving	–	52 (21.68)	67 (23.21)	0.45	**0.03**	0.24

Values are *n* (%). Bold means significant *p* values at <0.05 level. Typical symptoms include chest pain, sweating, vomiting, and shortness of breath.

Table 3
Median pre-hospital delay time in minutes in the study population, stratified by denial.

		Median delay			Median delay				
		In all patient		p	In women		p	In men		p
		N	Median		N	Median		N	Median	
Delay (min)	Denial	224	216 (104.5–808.5)	0.26	43	249 (120–1087)	0.22	181	196 (104–728)	0.46
	No Denial	309	200 (97–504)		91	213 (93–450)		218	182 (98–512)	
Delay between 3 and 24 h (min)	Denial	80	356 (240.5–686)	**0.02**	17	380 (249–644)	**0.05**	63	340 (240–692)	0.19
	No Denial	116	316.5 (223.5–484)		42	266 (213–359)		74	352 (224–504)	

Values are medians (25% quantile −75% quantile). Bold significant p values at <0.05 level.

demonstrated a borderline significant effect of denial on delay {Odds ratio: 1.12 (1.00–1.25), $p = 0.05$} [9]. Nevertheless, this study included only 177 patients (compared to 533 patients in the present analysis) and also accepted patients with NSTEMI and unstable angina (contrary to the present study with a homogeneous sample of STEMI patients).

A second interesting finding in the present investigation confirmed a clinically relevant median excess time of 40 min in deniers compared to non-deniers in the time window of 3 to 24 h (similar to the earlier studies [7,8]).

The examination of potential differences between the impact of denial on delay in the time window of <3 h and 3–24 h (and additionally in the delay time of >24 h) revealed that patients within the most favorable <3 h time window had experienced substantially higher symptom burden and symptom severity which suggests that the drastic suffering in the acute phase may have overcome the effect of denial on prehospital delay and psychological defense mechanisms may have become secondary [5,23] [24–27].

4.2. Protective effects of denial

The investigation also showed that denial was associated with lower levels of depressed mood, anxiety and with a higher level of well-being, thus confirming conceptual considerations that denial may provide psychological protection against negative affectivity [28]. Furthermore, our investigation disclosed that individuals with a higher level of denial tended to report less pain severity, racing heart and shortness of breath. The data did not provide any indications that deniers were different from non-deniers in terms of objective severity of the infarction: no significant difference emerged concerning length of intense care, incidence of cardiac arrest, or complications during the post-acute course. The frequency of recurrent infarctions was even higher in non-deniers. This is note-worthy because it is unlikely that the infarction in deniers was less severe.

4.3. The impact of denial on patients' behavior at STEMI onset

There is a general concern that denial may prompt the refusal to admit the clinical reality and thus deniers may fail to seek adequate medical attention and behavioral consequences confronting myocardial infarction [29] [30]. The present investigation is, to the best of our knowledge, the first to show in a large data set that the patients' reactions to symptom onset for deniers compared to non-deniers were not different in most aspects: the majority of both patient groups decided inadequately as their first reaction… *"To wait till the symptoms resolved"* (in about 60% of cases) and they *"tried to relax"* (in about 40% of cases). However, more deniers than non-deniers used to *"keep on continuing ongoing activities"* (which is a further non-adequate behavior) but there was also a strong tendency of deniers, yet not significant, to

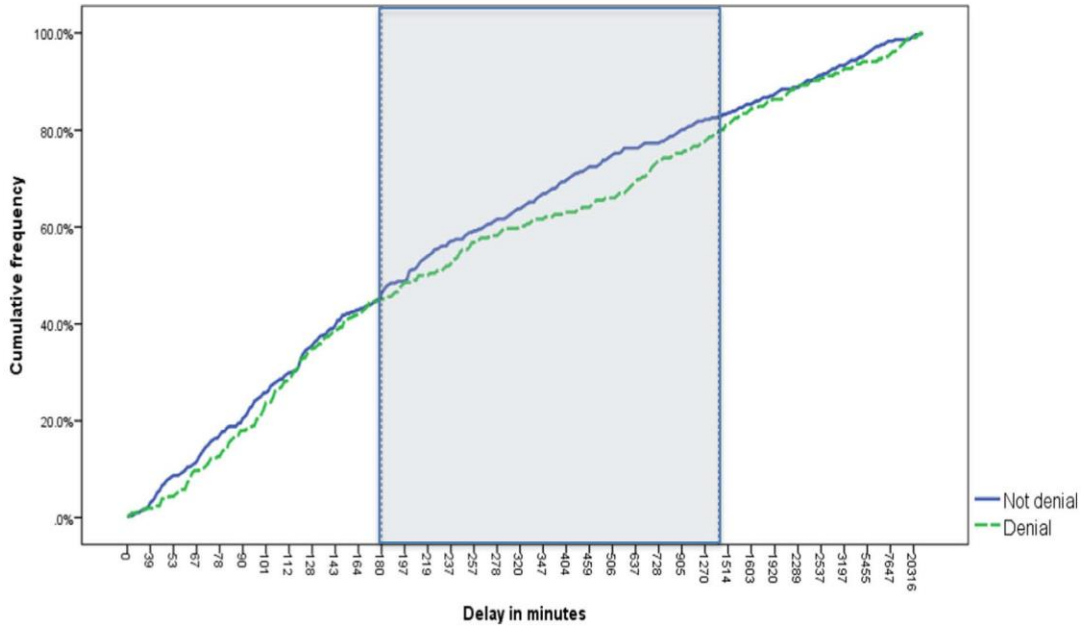

Fig. 2. Cumulative frequency distribution curves for prehospital delay among patients with (dash line) or without denial (solid line) in different time windows. There are no significant differences between patients with or without denial (Median: denial 216: vs. not denial 200 min; p value = 0.26). For patients who delayed between 3 h to 24 h, patients with denial delayed approximately 40 min longer than patients without. (Median: denial 356 vs. not denial 316.5 min; p value = 0.02).

Table 4
Symptom perception during acute myocardial infarction and subsequent delay times, stratified by 3 time windows.

		Delay time (n = 533)			
	Missing	Delay < 3 h	Delay 3–24 h	Delay > 24 h	p
typical symptom (≥3)	–	77 (31.95%)	50 (25.51%)	18 (17.71%)	**0.02**
symptom severity (≥3)	3	170 (70.54%)	104 (53.33%)	48 (51.06%)	**0.0001**
pain strength (>8)	8	128 (53.78%)	99 (51.30%)	45 (47.87%)	0.61

Values are n (%). Bold significant p values at <0.05 level.

activate the emergency ambulance system as their first step to release the chain of survival.

4.4. Characteristics of deniers

No other study so far has investigated the sociodemographic and clinical characteristics of a "typical" denier with a coronary heart disease condition. Deniers in the present study were more likely to be younger and to be male. Exactly these features are generally known to contribute to early arrival at the hospital [31]. This holds true also for a third significant characteristics of deniers; they are less likely to live alone, which likewise contributes to less delay [32,33].

5. Limitations

To our knowledge, this is the first study investigating the impact of denial on PHD in a strictly defined population (STEMI). There are a few study limitations that are worth considering. First, data on PHD were collected retrospectively, and thus there is a potential for recall bias. However, all data were collected at bedside within a very narrow time frame after STEMI. We had relatively small numbers of women, so replications of these results in larger datasets are warranted. Furthermore, selection bias could have resulted from excluding STEMI patients who died before reaching the hospital. The instrument we chose to measure denial did not cover overt denial items, which may have excluded patients with extreme denial, but the normal distribution of the denial score shows its ability to differentiate the denial level in cardiac patients.

6. Conclusion

Our study contributes important new findings to the role of denial in the face of an AMI in an extended data set of STEMI patients. First, the psychological coping mechanism of denial in the face of an AMI turned out to have more beneficial than adverse effects: denial contributed to less suffering from heart-related symptoms and negative potentially traumatizing affectivity without leading the patients to maladaptive behavior (e.g. waiting for the symptoms to resolve). In addition, from an overall perspective, denial only minimally increased the delay time, whereas in the time window of 3–24 h, denial led to a clinical significant longer delay. Apparently denial did not function in the most favorable time window presumably because of an extreme painful symptom pattern which overcame the effect of denial on prehospital delay. In this case, denial might be an intervention point for those who are without severe symptoms. However, this study was not designed for evaluating the long term consequences of AMI. Potential determinants of the relationship between denial and long term prognosis should be explored. Evidence shows that deniers were less likely to participate in post-AMI cardiac rehabilitation programs [29] or avoid cardio-protective health behaviors including treatment adherence [34,35]. Therefore, the concept of denial should be addressed in anamnestic interviews with patients in order to give advice for future behavior of patients at risk of a recurrent infarction.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jpsychores.2016.10.008.

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Conflicts of interest

None to declare.

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Chapter 7. Impact of anxiety (GAD) on prehospital delay of acute myocardial infarction patients?

Manuscript 2

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ORIGINAL PAPER

Impact of generalized anxiety disorder (GAD) on prehospital delay of acute myocardial infarction patients. Findings from the multicenter MEDEA study

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Abstract

Background Anxiety has been identified as a cardiac risk factor. However, less is known about the impact of generalized anxiety disorder (GAD) on prehospital delay during an acute myocardial infarction (AMI). This study assessed the impact of GAD on prehospital delay and delay related cognition and behavior.

Methods Data were from the cross-sectional Munich examination of delay in patients experiencing acute myocardial infarction (MEDEA) study with a total of 619 ST-elevated myocardial infarction (STEMI) patients. Data on socio-demographic, clinical and psycho-behavioral characteristics were collected at bedside. The outcome was assessed with the Generalized Anxiety Disorder scale (GAD-7). A GAD-7 score greater than or equal to 10 indicates general anxiety disorder.

Results A total of 11.47% ($n=71$) MI patients suffered from GAD. GAD was associated with decreased odds of delay compared to patients without GAD (OR 0.58, 95% CI 0.35–0.96), which was more significant in women (112 vs. 238 min, $p=0.02$) than in men (150 vs. 198 min, $p=0.38$). GAD was highly correlated with acute anxiety ($p=0.004$) and fear of death ($p=0.005$). Nevertheless, the effect remained significant after controlling for these two covariates. GAD patients were more likely to perceive a higher cardiovascular risk (OR 2.56, 95% CI 1.37–4.76) in 6 months before MI, which leads to the higher likelihood of making self-decision to go to the hospital (OR 2.68, 95% CI 1.48–4.85) in the acute phase. However, GAD was also highly associated with impaired psychological well-being, stress and fatigue ($p<0.0001$).

Conclusions In AMI patients, GAD was independently associated with less prehospital delay, but led to an impaired psychological state.

Keywords Generalized anxiety disorder · Behavior response · Decision time · Prehospital delay

X.Y. Fang and D. Spieler shared the first authorship.

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Abbreviations

AMI	Acute myocardial infarction
STEMI	ST segment elevation myocardial infarction
PHD	Prehospital delay
MEDEA	Munich examination of delay in patients experiencing acute myocardial infarction
CHD	Coronary heart disease
MACE	Major adverse cardiac event

Introduction

Anxiety and fear are closely related basic emotions. They comprise anticipatory affective, cognitive, and behavioral changes executed to avoid or reduce the impact of a potential threat or a danger [1]. A key difference between fear and anxiety rests in the certainty or uncertainty of the threat. Fear is the response to a rather certain and

objective threat, while anxiety is the response to a rather uncertain perceived subjective threat. Recent research has provided persuasive neurochemical and neuroanatomical evidence for this psychological distinction [2]. Once these anticipatory processes to uncertainty become maladaptive by being executed disproportionately to the likelihood or severity of the threat, pathological forms of anxiety develop, which can severely interfere with normal life [3, 4]. Anxiety disorders have been classified into several distinct disorders described in the DSM-5/ICD-10, one of which is referred to as generalized anxiety disorder (GAD) [5, 6]. With GAD, patients present with unfocused worry and anxiety that is not connected to recent stressful events. It is characterized by feelings of threat, restlessness, irritability, insomnia, tension, and physical symptoms such as palpitations, dry mouth, or sweating, lasting 6 month or longer. Due to the relapsing course of GAD, the disorder is often associated with seriously impaired social and occupational functioning. GAD is a common condition, with life time prevalence rates of 4–7% in the general population [7], women being twice as much affected [8]. In coronary heart disease (CHD) patients, its prevalence is even higher, ranging from 5.42 to 11.57% [9, 10].

Studies examining the impact of GAD on cardiovascular prognosis have yielded conflicting results: On one hand, GAD has been identified as an etiological risk factor of adverse cardiovascular events [11] such as ischemic stroke [12], myocardial infarction [9, 13]. On the other hand, recently several large scale studies show that GAD patients had a better prognosis following a cardiac event [14–17]. A probable reason for this positive effect of GAD might be due to higher alertness and increased health promoting behavior [15].

Time to treatment is a crucial determinant of survival in patients who have suffered an acute myocardial infarction (AMI) [18, 19]: the earlier interventional or thrombolytic therapy is given, the greater the reduction of infarct size and subsequent disability and mortality. Among numerous somatic and psychological factors which have the potential to influence delay time, it is already well-established that acute fear and anxiety during AMI onset reduce the decision delay to seek medical help [10, 11]. However, no study has been conducted so far to investigate the role of GAD on prehospital delay during AMI.

Thus, the objectives of our study are: (1) to assess the impact of GAD on prehospital delay and (2) to test whether a putative effect of GAD remains even after controlling for acute anxiety conditions, (3) to assess the impact of GAD on patient's behavioral responses to the symptoms during the acute phase of an AMI and (4) to further explore the impact of GAD on the post-acute course of AMI.

Methods

The multicenter, retrospective cross-sectional MEDEA study (Munich examination of delay in patients experiencing acute myocardial infarction) was conceived with the aim to evaluate prehospital delay of STEMI patients, and the factors which may contribute to prolonged delay.

Study design

The patients were recruited from eight different university or municipal hospitals with coronary care units, belonging to the Munich emergency system network clinics. The MEDEA study was approved by the Ethic Commission of the Faculty of Medicine of the Technische Universität München (TUM) on 10.12.2007 and the consent of the Munich Institut für klinische Forschung (IKF) for the participating four municipal hospitals (9.4.2008). The main inclusion criterion was diagnosis of STEMI as evidenced by typical clinical symptoms, ECG changes and myocardial biomarkers levels. Exclusion criteria were: In-hospital STEMI, resuscitation at AMI onset and language barriers or cognitive impairment impeding patients to answer the questionnaires properly. There were no age restrictions.

Standardized operation procedures (SOPs) were implemented to ensure the consecutive referral of eligible patients into the study. All patients were informed of the aim and procedures of the study and also that taking part in the study would have no effect on their treatment. All patients were required to sign a declaration of consent. Bedside interviews and self-administered questionnaires were conducted in the hospital ward within 24 h after referral from intensive care.

Sample

From 12 December 2007 until 31 May 2012, a total of 755 patients were screened for eligibility. In 619 patients, a diagnosis of STEMI was confirmed. Approximately, 18% of patients were excluded: 4% due to not meeting inclusion criteria and 14% due to absence of consent.

Data collection

The data collection process was divided into three sections. First, a structured bedside interview was conducted with trained personnel. Second, a self-administered questionnaire was filled by the patient without supervision. Third, data were collected from the hospitals' patient charts.

Measures

Prehospital delay (PHD)

Patients were asked to recall at what time acute symptoms began. The time difference between symptom onset and first ECG at hospital entry constitutes "prehospital delay" (PHD), measured in minutes. PHD was thus available as a continuous variable which was heavily left-skewed and did not approximate a normal distribution after log-transformations.

Generalized anxiety disorder

Anxiety was assessed with the German version of Generalized Anxiety Disorder scale (GAD-7). It is composed of 7 items, rated on a four-point Likert scale from not present to very high, leading to an overall score ranging from 0 to 21. A suspected diagnosis of GAD is defined by a GAD-7 score greater than or equal to 10. Using the threshold score of 10, the GAD-7 has a sensitivity of 82% for GAD [20].

Psychological measures

Depression was assessed with the Major Depression Inventory (MDI)—a self-report mood questionnaire able to generate an ICD-10 or DSM-IV diagnosis of clinical depression. The MDI contains 12 items. According to the DSM-IV definition, patients who had at least five symptoms in the MDI scale, of which at least one must be a 'core' symptom, were diagnosed with major depression [21].

Well-being was evaluated through the WHO-Five Well-Being index. It contains five items on a 6-point scale that range from 0 to 25. Thereafter, the raw scores are transformed into a scale that range from 0 to 100 [22].WHO-5 score less than or equal to 50 indicates suboptimal well-being [23]. Effectiveness of the index has been supported in evaluation of emotional well-being in patients with cardiovascular diseases.

Vital exhaustion was assessed using a four-item index on a five point Likert Scale that range from 0 to 16. Two items are from The Maastricht Questionnaire ("Do you often feel tired?" and "Do you often feel weak all over?"). The other two were obtained from the CES-D ("I felt that everything I did was an effort" and "I could not get going"). In present study, we applied the median split as a cut-off point, leading to an exhausted (>7) and non-exhausted (≤ 7) group. The predictive validity of the exhaustion index has been reported elsewhere as 3.18 and the internal consistency (Cronbach's) of this scale was 0.55 [24].

Psychological stress was assessed with three single-item questions relating to stress at work, at home and financial stress, rated on a four-point Likert scale, ranging from 3 (never) to 12 (permanent stress). Stress was defined as feeling irritable, filled with anxiety, or as having sleeping difficulties as a result of conditions at work or at home. In present study, we applied the median split as a cut-off point, leading to a stressed (>5) and non-stressed (≤ 5) group.

Patient behavioral responses to STEMI

A German version of the Response to Symptoms Questionnaire was applied [25], which assesses the behavior and subsequent reactions of both the patient as well as witnesses in the following areas: social context in which symptoms occurred and bystanders responses, behavioral responses to the symptoms, cognitive responses to the symptoms and emotional responses to the symptoms. The instrument also includes one item on symptom expectation, which measures the congruence between symptom expectation and perception (11 items, 5 point Likert scale, >3 rated was used as cut-off to define a high level).

Data analysis

Differences between dichotomous variables were assessed using the Chi square test. When comparing ordinal variables with more than two outcomes, the Mantel–Haenszel Chi square test was used. Differences in age were assessed using the t test. The nonparametric Wilcoxon test was used for assessing differences in median prehospital delay times. Multivariate Logistic regression model was applied to assess the association between GAD and patients' responses to the symptom onset. In addition, the additional effect of stress and exhaustion on patients' responses was also assessed by logistic regression model. Because anxiety level is highly correlated with other psychometric factors, logistic regression with different grades of adjustments for psychological factors was applied to assess the association between GAD and the chance of longer delay. Patients who delayed more than two hours are defined as delayed group. Adjustments were made for fear of death, acute anxiety during the symptom onset (model 2), and additionally for stress (model 3), exhaustion (model 4) and depression (model 5).The relative risk for longer delay is presented as odds ratio (OR) with 95% confidence interval (95% CI).

All statistical analyses were run in SAS (Version 9.3, SAS-Institute Inc., Cary, NC, USA). The significance level was set at $p<0.05$. The analysis and description in this paper follow the STROBE guidelines for cross-sectional studies [26].

Table 2 The impact of GAD, further stratified for GAD population with stress ($n=56$) and exhaustion ($n=53$)

	GAD vs. no GAD (71 vs. 548) OR (95% CI)	GAD with stress vs. others (56 vs. 457) OR (95% CI)	GAD with exhaustion vs. others (53 vs. 566) OR (95% CI)
Cognitive responses			
Heart misattribution	1.00 (0.61–1.65)	1.01 (0.58–1.75)	0.97 (0.55–1.71)
Failed to recognize the symptoms as MI	1.32 (0.81–2.17)	1.51 (0.87–2.63)	1.47 (0.83–2.59)
Insufficient risk perception	**0.39 (0.21–0.73)**	**0.32 (0.16–0.61)**	**0.36 (0.18–0.72)**
Behavioral responses			
Take medicine	0.86 (0.52–1.44)	1.06 (0.52–2.17)	1.29 (0.59–2.81)
Wait until the symptom resolves	0.70 (0.43–1.16)	0.69 (0.39–1.19)	0.90 (0.50–1.61)
Continue doing the ongoing activity	1.01 (0.54–1.88)	1.03 (0.52–2.06)	1.06 (0.52–2.18)
Try to relax	1.25 (0.75–2.10)	1.05 (0.60–1.85)	1.45 (0.79–2.63)
Call someone for help	2.32 (0.55–9.88)	1.80 (0.42–7.68)	1.65 (0.39–7.07)
Call general physician	0.95 (0.41–2.17)	1.41 (0.49–4.05)	1.29 (0.45–3.72)
Call emergency doctor	1.24 (0.75–2.05)	1.21 (0.69–2.12)	1.52 (0.86–2.69)
Used ambulance to get to the hospital	0.86 (0.52–1.44)	0.90 (0.51–1.59)	0.76 (0.42–1.38)
Drive themselves to the hospital	1.28 (0.68–2.41)	1.16 (0.58–2.31)	1.63 (0.75–3.55)
Made self-decision to go to the hospital	**2.68 (1.48–4.85)**	**2.89 (1.46–5.70)**	**2.67 (1.35–5.29)**
Post-acute course			
With complication	**0.44 (0.20–0.99)**	0.60 (0.26–1.35)	0.43 (0.17–1.10)*
Cardiac arrest	2.11 (0.76–5.84)	**2.81 (1.01–7.83)**	0.97 (0.00–4.24)
Intensive care ≥ 3 days	0.91 (0.54–1.52)	0.95 (0.53–1.68)	0.89 (0.50–1.59)

Bold means significant p values at <0.05 level

*$p=0.08$

Table 3 Association of GAD and prehospital delay assessed by logistic regression, adjusted by fear of death, acute anxiety, stress, exhaustion and depression

Emotional factors	Delay > 2 h vs. delay ≤ 2 h (426 vs. 193) OR (95% CI)				
	Model 1	Model 2	Model 3	Model 4	Model 5
GAD	**0.58 (0.35–0.96)**	**0.60 (0.35–0.99)**	**0.48 (0.27–0.84)**	**0.49 (0.27–0.89)**	**0.50 (0.26–0.97)**
Fear of death		0.64 (0.33–1.24)	0.77 (0.35–1.67)	0.77 (0.35–1.67)	0.78 (0.36–1.71)
Acute anxiety		0.96 (0.91–1.01)	0.96 (0.90–1.02)	0.96 (0.90–1.02)	0.96 (0.90–1.01)
Stress			1.05 (0.94–1.18)	1.05 (0.94–1.18)	1.04 (0.93–1.12)
Exhaustion				1.01 (0.67–1.52)	0.98 (0.67–1.50)
Depression					1.00 (0.44–2.26)

Bold means significant p values at <0.05 level

All the models were adjusted for sex and age

Model 1: the crude model

Model 2: adjusted with acute anxiety condition (including fear of death and acute anxiety)

Model 3: further adjusted with self-perceived burden of daily stress

Model 4: further adjusted with vital exhaustion

Model 5: further adjusted with depression

The post-acute course of patients with GAD

In the post-acute infarction phase during ICU stay, patients with GAD were less likely to have complications (OR 0.44, 95% CI 0.22–0.99). The GAD patients additionally suffering from stress were more likely to experience in-hospital cardiac arrest, but did not show differences regarding complication and ICU stay compared to their counterparts. GAD

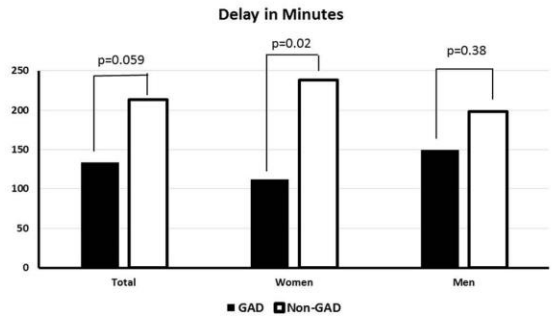

Fig. 1 Nonparametric test for comparing median delay time (in min) for all patients with and without GAD and stratified for women and men

patients suffering additionally from vital exhaustion tended to experience less cardiac complications (OR 0.43, 95% CI 0.17–1.10).

Discussion

To the best of our knowledge, this is the first comprehensive evaluation of the impact of GAD on prehospital delay in patients facing an AMI. The major finding of the present study is that GAD had a favorable effect on reducing prehospital delay during AMI. This effect of GAD on prehospital delay was significant in women, while in men, we identified solely a non-significant trend. Moreover, GAD was associated with better prognosis in the post-acute phase of AMI.

Patients suffered from GAD also presented a comorbidity pattern of impaired mental health, meaning the patients with GAD were also significantly more likely to suffer from acute anxiety, depression, vital exhaustion and perceived stress. It has been well-documented that pronounced acute anxiety/fear owing to the sudden onset of the life-threatening AMI leads to a shorter delay time, hereby favoring a good prognosis [27–29].

Of note, the beneficial effects of GAD on prehospital delay and prognosis found in our homogeneous STEMI sample remained significant even after we controlled for acute fear of death [30], depression, exhaustion and perceived stress. This finding underscores that GAD is a powerful and independent protective factor on its own in patients facing an AMI.

This is a remarkable finding, which points to a specific alertness of GAD patients more likely to be present at the time long before the onset of AMI. This assumption is supported by our finding showing that GAD patients had a higher self-perceived MI risk than non-GAD patients. In that line, GAD has been found to be a 'driver' for individuals to address their health needs more regularly and conscientiously and seek help at the early signs of the disease. Dubayova et al. [31] reported in a systemic review including 15 studies that being 'anxious' has a significant positive effect on decision making in help-seeking behavior. Parker et al. [14] found that GAD patients received more medical tests and tended to take part more often in post-AMI rehabilitation programs. Interestingly, GAD patients did not experience a different pattern of acute symptoms compared to non-GAD patients. This is noteworthy because it is unlikely that the GAD patients sought help faster because of more severe symptoms.

Moreover, the study reveals the association of GAD patients with a better prognosis in the post-acute phase of AMI. It is not unlikely that this is a consequence of the reduced delay time in GAD patients as well, based on the earlier treatment and hereby improved course with less symptoms, since every minute of delay to treatment for STEMI has previously been shown to affect the 1-year mortality [32]. Yet, the post-acute outcome was not favorable anymore, if GAD was accompanied by stress or exhaustion (Table 2).

Contrary to expectation, we found no sex difference of GAD prevalence in our clinical sample. This is remarkable because in general population, women are twice as much affected with GAD than men [8]. The analysis shows a sex-specific impact of anxiety on delay time though. In women, the difference of delay time was highly significant, whereas in men, there was only a trend towards a reduced delay. Currently, we have no possible reasons to explain the differences.

Although this study identified favorable effects in patients meeting GAD criteria having shorter time to treatment and fewer complications, it seems to be essential to balance this 'advantage' with the disease burden of GAD itself: GAD patients were more likely to suffer from higher levels of negative emotions (including depression, exhaustion and perceived stress and thus impaired psychological well-being). This is in line with the observation showing that anxiety and depression frequently co-occur [33, 34].

To our knowledge, this is the first study investigating the impact of generalized anxiety disorder on prehospital delay in a strictly defined population of STEMI patients. There are a few study limitations that are worth considering. First, all data were collected at bedside within a very narrow time frame (< 24 h after referral from intensive care) after STEMI, nevertheless, we cannot fully exclude the possibility of recall bias. We had relatively small numbers of women, so replications of these results in larger datasets are warranted. Furthermore, selection bias could have resulted from excluding STEMI patients who died before reaching the hospital. Finally, GAD diagnosis was based on GAD-7 questionnaire data which provides a sensitivity of 82% for GAD [35] using a threshold score of 10.

Conclusion

Our study demonstrates that in patients facing an AMI, GAD is associated with an increased chance of early arrival and thus had fewer complications, despite its known adverse effects on psychological well-being. The higher perceived MI risk and the higher chance of making self-decision to seek medical help in GAD patients suggests that GAD patients are particularly sensitive to early sign of the disease, ultimately resulting in shorter time to treatment and better prognosis. The shorter delay time and appropriate behavioral responses during AMI indicated the protective effect of GAD on patients' acute situation. However, our study does not provide information regarding long-term effect of GAD on patients' cardiac outcome. Further investigation is necessary to reveal whether the impaired psychological well-being caused by GAD will be detrimental for long term prognosis. This will provide necessary clinical implication for the appropriate timing to intervene GAD in CHD patients.

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Compliance with ethical standards

Conflict of interest None to declare.

Ethic statements All patients were informed of the aim and procedures of the study and also that taking part in the study would have no effect on their treatment. All patients were required to sign a declaration of consent. Details that might disclose the identity of the subjects under study has been omitted.

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