# Taking heartache to heart;

Empirical psychological modelling of chest pain

A.W. Serlie

# Taking heartache to heart;

Empirical psychological modelling of chest pain

Hartepijn ter harte genomen;

Empirisch psychologisch modelleren van pijn op de borst

Proefschrift

ter verkrijging van de graad van doctor

aan de Erasmus Universiteit Rotterdam

op gezag van de Rector Magnificus

Prof. Dr. P.W.C. Akkermans M.A.

en volgens het besluit van het college voor promoties

de openbare verdediging zal plaatsvinden op

woensdag 12 juni 1996 om 13:45

door

Alexander Willem Serlie

Geboren te Vlaardingen

**Promotie-commissie**

Promotoren: Prof. Dr. J. Passchier
Prof. Dr. J.R.T.C. Roelandt

Overige leden: Prof. Dr. M.L. Simoons
Prof. Dr. W.J. Schudel
Prof. Dr. A.H.C. van der Heijden

Co-promotor: Dr. R.A.M. Erdman

Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

ISBN 90-9009550-0
Key Words: Cardiac phobia, Anxiety

Cover by S. King Thomas

*To Jantina*

# Table of Contents

# 1. Introduction

The chest pain of patients visiting a cardiology out-patient's clinic is most often caused by coronary atherosclerosis, which induces an oxygen shortage in the heartmuscle and thereby pain. However, in approximately 30% of the chest pain patients no clear somatic cause can be found. Contemporary literature (e.g. (1) refers to these patients as suffering from cardiophobia. For a closer look at this disorder it is imperative to understand the different types of chest pain and the various possible causes of it.

As far as the type of chest pain is concerned a difference can be made between chest pain typical, atypical and nontypical for angina pectoris. *Typical chest pain* is diagnosed when there is a 1) substernal chest pain or pressure, 2) usually brought on predominantly by exertion, emotion or temperature changes and 3) relieved promptly at rest or with nitroglycerine. Chest pain is considered to be *atypical* when only two of the three factors are present and when only one characteristic is present the chest pain is considered *nontypical* (see e.g. (2).

**Table 1.1** *Differential diagnosis of chest pain*

| Organic | | Non-organic |
|---|---|---|
| Cardiac | Non-cardiac | |
| coronary atherosclerosis | oesophageal reflux | cardiac anxiety |
| small vessel disease | Tietze's syndrome | |
| aortavalvestenosis | Cervical spinal cord | |
| mitralvalveprolaps | pain of the upper extremity | |
| hypertrophic cardiomyopathy | exercise asthma | |
| pericarditis | | |

The cause of the patient's chest pain can either be cardiac or non-cardiac. Cardiac chest pain can, for example, be caused by coronary atherosclerosis, small vessel disease, aortavalvestenosis, mitralvalveprolaps, hypertrophic

cardiomyopathy or pericarditis. In the case of non-cardiac chest pain an other than cardiac disorder causes the chest pain, for example oesophageal reflux, Tietze's syndrome, cervical spinal cord, pain of the upper extremity, exercise asthma. When no cardiac or other organic cause can be found for the chest pain, the pain is considered to be 'generated' by cardiac anxiety (3). The symptoms of hyperventilation, which can be related to chest pain, can either be organic, e.g. a lung embolism, or non-organic. Sometimes cardiovascular abnormalities can be found which appear not to be related to the presence of chest pain. In these patients no subjective improvement is found even after the coronary abnormalities have been treated (see e.g. (4). The complexity of the problem of chest pain increases when the causes being organic and nonorganic interact.

In the studies combined in this thesis we focused on the psychological comparison between the patients with cardiac chest pain caused by coronary atherosclerosis and patients with non-cardiac, non-organic chest pain complaints. In particular, our interest was to what extent a non-cardiac diagnosis can be predicted by the use of psychological tests chosen on the basis of previous literature (5-9).

For the prediction of the presence or absence of coronary artery disease, the type of chest pain and age and gender are important variables to consider. In a review of the literature Diamond and Forrester (10) noted that the classification of chest pain is reflected by a different prevalence of coronary artery disease per category. The prevalence of disease in persons with typical angina is about 90 per cent, whereas atypical angina shows a 50 per cent prevalence and non-anginal chest pain a 16 per cent prevalence. Diamond and Forrester (10) showed that when patients are classified according to age and gender; the prevalences range from 0.3 per cent for women between 30 and 39 years of age and more than 12 per cent for men aged between 60 and 69. Combining symptoms and age and gender using a conditional probability analysis the authors concluded that the pre-test likelihood in a 55-year old man with typical angina is 92 per cent, but the likelihood in a 35 year old woman with atypical angina is only 4 per cent. As noted these figures can be derived from only three basic characteristics: type of chest pain, age and gender. Performing various diagnostic tests will increase the likelihood of an accurate diagnosis. Diamond and Forrester (10) for example showed that a 45 year old man with

atypical angina has a pretest likelihood of coronary artery disease of 46 per cent. If the patient shows a 1.0 mm depression of the S-T segment after a electrocardiographic stress test, the post-test likelihood will be 64 per cent. A 2.5 mm depression of the S-T segment would correspond with a 97 per cent post-test likelihood. When the post-test likelihood is less than 20% a patients is considered to have no coronary artery disease. A post-test likelihood of more than 80% gives reason to believe the patient has a coronary artery disease. Between 20% and 80% more diagnostic testing is required.

From the above we can conclude that one can diagnose the presence of coronary artery disease (CAD) fairly accurately with only a few variables. The interesting question remains, however, in which way chest pain patients without a cardiac or an other organic cause for their complaints (NCA) differ from CAD patients.

The objective of the studies combined in this thesis was to study the psychological and demographical characteristics of two groups of chest pain patients; patients with a cardiac (CAD) and patients with a non-cardiac, non-organic (NCA) cause for their chest pain. With the knowledge of previous literature (5-9) we expected there to be considerable differences between these groups. Once having established these differences our aim was to construct a diagnostic instrument in the form of a quantative model. With this instrument non-cardiac chest pain with a clear psychological component could be recognised more easily and in an earlier stage of diagnostic testing.

Our second objective was to study patients over time as to see whether the differences between both patient groups remain the same and if so if this should have implications for treatment of the NCA patients.

The studies in this thesis and therefore the constructed models, can only be seen as a first stage in the quantification of the psychological profiles of patients with non-cardiac chest pain, as the studies were not set up as standardised experiments. Our aim was to gather data within the limitations of daily clinical practice, with the least extra strain on patients. Limitations of our studies lie in the fact that the patients were only seen at the Rotterdam University Hospital, which might encompass a certain selection bias, compared to other non-academic hospitals. The data can therefore only be used as a first step and need further additional confirmation by future investigations.

In chapter 2 a review of the contemporary literature will be given and possible explanations for the relationship between complaints and non-cardiac findings presented. Furthermore, the ability of predicting non-cardiac chest pain from psychological factors and a range of follow-up studies will be discussed. Finally the possibilities of treating cardiac phobia are mentioned.

Chapter 3 deals with a first explorative study of the differences between cardiac and non-cardiac patients. The psychological differences between the two patient categories are determined, on average, 1.3 years after their initial visit to their treating cardiologist and an attempt is made to construct a model which can predict a patient either being cardiac or non-cardiac.

Chapter 4 continues the line set out in chapter 3 but focuses on chest pain patients visiting the cardiology out-patient's clinic for the first time, without any knowledge of their final diagnosis. This is the main group of interest for which an instrument was designed to measure the psychological characteristics which differentiate the groups with and without a cardiac diagnosis. Here too, an attempt is made to construct a model based on psychological characteristics with which a patient's chest pain complaints can be predicted to being non-cardiac or not.

Chapter 5 is a follow-up study of the patients reviewed in chapter 4. Like the study in chapter 3 the patients were familiar with the outcome of their cardiologic testing and were seen on average 1.6 years after their first visit to the out-patient's clinic. In this study, however, it was possible to assess the performance of and the variables contributing to the predictive model over time.

In chapter 6 a closer look is taken at the psychological factors underlying non-cardiac chest pain. By means of the structural equation modelling technique LISREL a model of the various variables associated with chest pain is constructed for both the non-cardiac as well as the cardiac patients.

Finally, in chapter 7 the outcomes of the different studies, the similarities and the differences will be discussed. A comparison of the new body of evidence in relation to what was already known, will be carried out. Furthermore, the limitations of the conducted studies will be discussed and recommendations for future research made.

Finally, in chapter 8 a summary of the studies in this thesis is given.

In the appendices, the principles of logistic regression analysis and structural equation modelling will be explained. Additionally, the items of the subscales significantly contributing to the predictions models will be presented in the form of a diagnostic instrument. This diagnostic instrument should comply to being reliable, valid, short and easy to use in clinical practice

## 1.1 References


1. Eifert GH. Cardiophobia: a paradigmatic behavioural model of heart-focused anxiety and non-anginal chest pain. Behav Res Ther 1992; 30(4): 329-345.
2. Beitman BD, Basha I, Flaker G, et al. Atypical or nonanginal chest pain. Panic disorder or coronary artery disease? Arch Intern Med 1987; 147(9): 1548-1552.
3. Manger Cats V. [Anamnesis, physical examination and the diagnostic process]. In: Roelandt JRTC, Lie KI, Wellens HJJ, Van de Werf F, ed. [Text-book Cardiology] Leerboek cardiologie. Houten/Diegem: Bohn Stafleu Van Loghum, 1995: 696.
4. Booth DC, Deupree RH, Hultgren HN, DeMaria AN, Scott SM, Luchi RJ. Quality of life after by-pass surgery for unstable angina. 5-year follow-up results of a Veterans Affairs Cooperative Study. Circulation 1991; 83(1): 342-344.
5. Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med. 1984;14(1): 51-61.
6. Channer KS, Papouchado M, James MA, Rees JR. Anxiety and depression in patients with chest pain referred for exercise testing. Lancet 1985; 2(8459): 820-823.
7. Beitman BD, Basha I, Flaker G, DeRosear L, Mukerji V, Lamberti JW. Major depression in cardiology chest pain patients without coronary artery disease and with panic disorder. J Affective Disord 1987;13(1):51-59.
8. Katon W, Hall ML, Russo J, et al. Chest pain: relationship of psychiatric illness to coronary arteriographic results. Am J Med 1988;84(1):1-9.
9. Cormier LE, Katon W, Russo J, Hollifield M, Hall ML, Vitaliano PP. Chest pain with negative cardiac diagnostic studies. Relationship to psychiatric illness. J Nerv Ment Dis 1988;176(6):351-358.
10. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Eng J Med 1979;300:1350-1358.

# 2. Psychological aspects of non-cardiac chest pain

*A.W. Serlie, R.A.M. Erdman, J. Passchier, R.W. Trijsburg and F.J. ten Cate*
*(Psychotherapy and Psychosomatics, 1995;64:62-73[1])*

## 2.1 Abstract

Approximately 30% of patients visiting a cardiologist for the first time with complaints of chest pain appear to have normal coronary arteries. These patients generally have a higher prevalence of atypical chest pain, are relatively young, often female, in most cases suffer from panic disorder and have high scores on depression and anxiety scales. In this article some of the recent studies conducted in this particular line of research are reviewed and some possible explanations for the relationship between complaints and non-cardiac findings are presented. Furthermore, the ability of predicting non-cardiac chest pain from psychological factors and a range of follow-up studies are discussed. Finally the possibilities of treating cardiac phobia are mentioned.

## 2.2 Introduction

Over the past decades a considerable amount of research has been conducted into the disorders which are collectively best known as Da Costa's syndrome. In a review by Paul (1), a nice enumeration of Da Costa's syndrome characteristics is given; which is often familial, characterised by the presence of one or more symptoms including breathlessness with and without effort, palpitation, nervousness, chest discomfort not typical of angina pectoris caused by ischaemic heart disease, fatigability, and faintness; tending to occur in attacks which may recur over years and for which there is no specific treatment.

Hartstone (2) and Stillé (3) were among the first pioneers in researching the disorder, observing the conditions among soldiers, they respectively referred to the disorder as "muscular exhaustion of the heart" and "palpitation". Hartstone

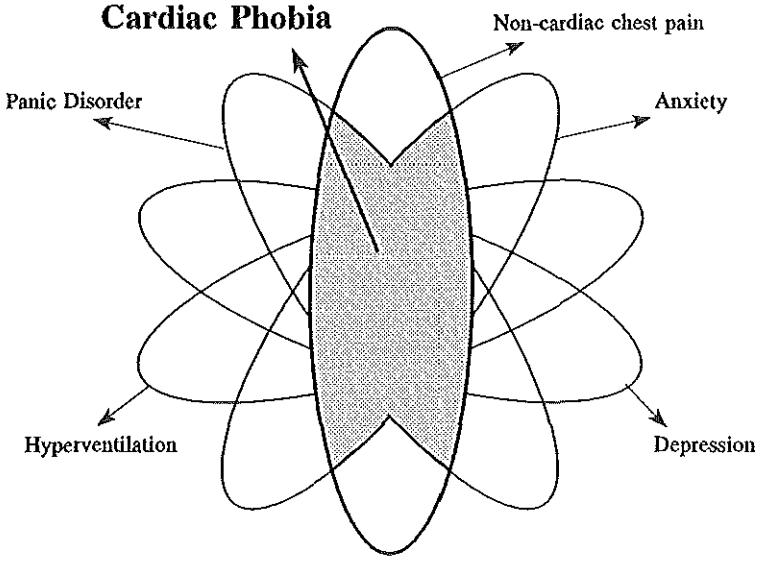
---

attributed the disorder to stress of the military campaigns with great and prolonged exertion with the most unfavourable conditions possible -privation of rest, deficient food, bad water and malaria. Maclean (4) ascribed the disorder to the excessive effort of carrying the soldier's field pack and by the manner in which its straps constricted the circulation. In 1871, a former military physician, Da Costa (5) introduced the term "irritable heart" for what he described as a "peculiar form of functional disorder". Subsequently the extensive disorder was named "Da Costa syndrome". Lewis (6) pointed out that the syndrome also could be found in civilian as well as military life. He introduced the term "effort syndrome", believing that all clinical features were those normally produced by effort but in these soldiers occurred on very slight effort. The term "neurocirculatory asthenia" was first introduced by Levine (7) in 1917, as an american team of military physicians did not accept the term effort syndrome and did not want to include the word "heart" because of its psychological effect. In 1958 Kannel (8) presented criteria for defining neurocirculatory asthenia which included respiratory complaints combined with either one or more symptoms from two of the following symptom groups: a) palpitations, chest pain and chest discomfort; b) nervousness, dizziness, faintness, discomfort in crowds; c) undue fatigability or tiredness, or limitation of activities. Fava and colleagues (9) further studied the term neurocirculatory asthenia as defined by Kannel (8), but they made a further distinction in primary and secondary neurocirculatory asthenia. In the former, neurocirculatory asthenia was a primary illness, not to be explained on the basis of a mental disorder. In the latter, the neurocirculatory asthenia was secondary to a mental disorder. Patients suffering from primary neurocirculatory asthenia, compared with normal healthy subjects in the general population, did not report significantly more anxiety, phobic symptoms or abnormal illness behaviour, except for observer-rated depression. On the basis of their results they thought it better to discard the term neurocirculatory asthenia and remain with the term Da Costa's syndrome.

Most of the recent Anglo-Saxon literature has, however, abandoned the terminology previously mentioned and has focused primarily on chest pain. These studies have shown that in some cases more than half of the patients undergoing cardiac catherization or treadmill testing, because of chest pain, have normal or minimally diseased coronary arteries (10-21). These patients are generally relatively young, often female, in most cases suffer from panic

disorder, hyperventilate, have high scores on depression and anxiety scales and a higher prevalence of atypical chest pain. Focusing on these complaints, patients are nowadays frequently classified as cardiac phobics or cardiac neurotics (10, 12, 14-16). Figure 2.1 shows an adapted model by Bass and Wade (10) describing the main factors contributing to cardiac phobia.

**Figure 2.1** *Factors contributing to cardiac phobia; extension of the Venn diagram proposed by Bass and Wade (10), showing the overlap between non-cardiac chest pain, anxiety, depression, Panic Disorder and hyperventilation.*




Before reviewing studies on cardiac phobia, we will present some imperative definitions for clearly understanding the major problems related to cardiac phobia, because even after undergoing extensive testing, and being told that "nothing is wrong" a considerable number of patients persist in having chest pain complaints (see paragraph on follow-up studies). In order to prevent unnecessary suffering and unduly high workload for doctors and staff, not to mention the large cost-factor (22), early detection of the disorder is crucial.

Eifert (23) defines *cardiac phobia* as an anxiety disorder of persons characterized by repeated complaints of chest pain, palpitations, and other somatic sensations accompanied by the fear of having a heart attack and of dying. Persons with cardiac phobia focus attention on their heart, when experiencing stress and arousal, and, therefore, they tend to perceive its function in a phobic

manner, and continue to believe they suffer from an organic heart problem despite repeated negative results from medical testing.

Panic disorder appears to be firmly associated with psychosomatic complaints (24-26). According to DSM-III-R (27), *panic disorder* is diagnosed in individuals experiencing at least four panic attack periods (each including a minimum of four symptoms such as shortness of breath, choking, palpitations or accelerated heart rate) in a 4-week period that are not sustained by any organic factor (e.g. hyperthyroidism, reaction to caffeine or other stimulants), and that do not occur exclusively on exposure to a specific phobic stimulus.

In the studies mentioned, *atypical* chest pain is considered present when some unusual feature such as location, duration of pain, consistency of relation to physical exertion or emotional stress was described, but at some time the pain has been related to physical or emotional stress (28). *Typical* chest pain is diagnosed when there is a substernal chest pain or pressure, usually brought on predominantly by exertion, emotion or temperature changes and relieved promptly at rest.

In this article we will review the most important psycho-medical studies, appearing in the Medline and PsycLIT databases, using the keywords "chest pain", "normal coronary arteries", "cardiac neurosis", "cardiac phobia", "neurocirculatory asthenia" and "psychological", The studies were all conducted after 1980. Furthermore, because of the importance of early detection and differentiation, we will only discuss those studies in which patients with chest pain and normal coronary arteries were compared with patients with chest pain of a somatic nature. We will focus on the psychological and psychiatric disorders that may accompany non-cardiac chest pain and try to generate some explanations for the symptoms. Finally we will present possibilities of predicting non-cardiac chest pain, using patient characteristics, also in the long run and mention different forms of therapy.

## 2.3 Psychological and psychiatric disorders

As stated earlier and as can be seen in Table 2.1, where nine studies are summarized, psychological and psychiatric disorders appear to play a major part in the search for an explanation of cardiac complaints without a somatic cause.

In 1983, Bass and associates (29) investigated psychiatric morbidity and unexplained breathlessness in 99 patients with normal and abnormal coronary arteries. All patients were suffering from chest pain and underwent coronary arteriography. Consequently, the patients were divided into three groups; group I with normal coronary arteries, group II with slight CAD (up to 50% obstruction of any vessel) and group III with significant CAD (50% or more obstruction in one or more vessels). They discovered that significantly more patients in groups I (58%) and II (67%) had psychiatric morbidity than those in group III (23%; $p < 0.01$) and that anxiety neurosis was the most commonly occurring diagnosis in groups I and II. Furthermore patients in group I ($\bar{x} = 44.5$) were significantly younger than those in groups II ($\bar{x} = 49.9$) and III ($\bar{x} = 51.4$).

In an article one year later, Bass and Wade (10) concluded that their findings indicated that approximately two thirds of patients with normal and near normal arteries had predominantly psychiatric rather than cardiac disorders. The symptoms in these patients were more likely to represent the somatic manifestations of anxiety and overbreathing than the consequences of underlying cardiac disease. Examining the clinical and psychological characteristics, group II (up to 50% obstruction of any vessel) patients highly resembled the patients of group I (normal coronary arteries). The results also indicated that group I patients were less likely to be employed and less likely to be married at the time of angiography than patients of the other two groups. Furthermore patients in groups I and II were significantly receiving more psychotropic drugs than patients in group III. Men with insignificant coronary lesions had higher scores of neuroticism and extraversion than men with significant coronary lesions.

In a study by Katon and associates (15), the relationship between psychiatric illness and arteriographic results was investigated. Seventy-four patients with chest pain but no prior history of organic heart disease participated in this study. On the basis of coronary arteriography results, a division was made between patients with Normal Coronary Arteries (NCA) and patients with Coronary Artery Disease (CAD). The results indicated that patients with chest pain and a negative coronary arteriogram were significantly younger and more likely to be female than patients with chest pain and a positive arteriogram. Table 2.1 shows that NCA patients had a higher score for major depression, anxiousness, panic disorder and suffered from multiple phobias.

Lantinga and colleagues (18) studied 24 patients with angiographically determined NCA and psychosocially compared them with 24 matched patients with a positive angiogram. The patients with normal coronary arteries had significantly higher scores on various anxiety and depression questionnaires than the coronary artery disease patients .

Cormier and co-workers (16) studied 98 patients with a chief complaint chest pain, but no prior history of organic heart disease, and whose chest pain was thought suspicious enough to warrant cardiac testing. On the basis of either coronary arteriography ($n_1=73$) or exercise treadmill testing ($n_2=25$), the patients were diagnosed as having NCA or CAD. The results again indicated that patients with NCA were more likely to be female, younger in age, to report atypical chest pain more often, and to mention a greater number of autonomic symptoms on a Diagnostic Interview Schedule (DIS). The patients in the NCA group had a significantly higher prevalence of major depression, panic disorder and multiple phobias than did the CAD group. Based on their data they concluded that a young woman (42 years of age) with atypical chest pain and panic disorder had a 99% probability of a negative cardiac test (regardless of method of testing), while an elderly woman (68 years of age) with typical chest pain and panic disorder had a 78% probability of a negative arteriography test. For men the figures were 94% and 25% respectively.

No significant difference between cardiac and non-cardiac patients, was, however, found by Mayou (21) on anxiety and depression scores. Although general practitioners and cardiologists recognised significantly ($p < 0.05$) more psychological problems among the non-cardiac patients.

Beitman and co-workers (25) conducted a study of 103 patients with atypical or non-anginal chest pain in relationship to panic disorder. From their study they concluded that panic disorder does not "cause" chest pain, but only that atypical and nonanginal chest pain are likely to be associated with panic disorder.

In another study by Beitman (26) the occurrence of panic disorder in patients with chest pain and angiographically normal coronary arteries was investigated. By means of the Structured Clinical Interview Schedule panic disorder was diagnosed; this resulted in 32 (34%) of the 94 subjects meeting the criteria for panic disorder. Furthermore all subjects were asked to complete various self-assessment tests to measure aspects as depression, anxiety and fear. The patients were divided into two groups; those with panic disorder (PD) and those

without panic disorder (NPD). As far as the demographic data are concerned a significant difference was found between the two groups for age. On the self-assessment tests the panic disorder (PD) group scored higher on the variables psychoticism, somatisation, depression, hostility, anxiety and paranoia, than the patients without panic disorder (NPD).

Recently Alexander and colleagues (20) provided evidence that cardiac phobia does not only occur in western cultures, but also in countries such as India. In their study, consisting of male patients only, they too found that the NCA group was significantly younger ($\bar{x}_{nca} = 28$ vs $\bar{x}_{cad} = 56$ years), and suffered more from panic disorder and major depression.

Concluding from the studies mentioned, one can deduce that psychiatric and psychological rather than somatic disorders occur more frequently in patients with chest pain without, than in chest pain patients with diseased coronary arteries.

## 2.4 Possible explanations

Next to psychological explanations, some researchers, however, do consider the possibility of explaining cardiac phobia in somatic terms. In a study by Gasic (30) patients suffering from non-cardiac chest pain appeared to respond to psychological stress by an inadequate sustained activation of the sympathetic nervous system.

Cannon (31) discussed the possibility of non-cardiac chest pain being due to myocardial ischemia induced by abnormalities of the coronary microcirculation or arteries too small to be imaged by current arteriographic techniques. In a later study he referred to this condition as *microvascular angina* (32).

Katon (15) discussed biological studies in which physiologic changes may explain the mechanism by which panic disorder produces cardiac symptoms (see also Katon et al. (33)). According to Katon, the constellation of panic symptoms is believed to be caused by an excess of central noradrenergic activity. The panic attack is similar to the flight-or-fight response, in that the person physiologically is prepared for danger, but the attacks occur spontaneously without any external threat (24).

Problems of an oesophageal nature might also lead to angina-like chest pain. In a review by Davies (34), it was concluded that 30% of the patients with non-cardiac chest pain have this pain due to an oesophageal cause.

**Table 2.1**: *Characteristics of patients with NCA or CAD*

| Ref First author | n | | Female (%) | | Typical Pain (%) | | Depression (%) | | Anxiety (%) | | Panic disorder (%) | | Simple Phobias (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NCA | CAD | NCA | CAD | NCA | CAD | NCA | CAD | NCA | CAD | NCA | CAD | NCA | CAD |
| (10) Bass | 46 | 53 | 43 | 23 | 30 | 79 | 7 | 8 | 37 | 2 | - | - | - | - |
| (12) Channer | 37 | 50 | 32 | 12 | 27 | 88 | 16 | 6 | 30 | 8 | - | - | - | - |
| (25) Beitman | 73[1] | 0 | 71 | 40 | - | - | [2] | - | -[3] | - | 59 | 53 | 19 | 7 |
| (15) Katon | 28 | 46 | 54 | 17 | 26 | 89 | 36 | 4 | -[4] | - | 43 | 7 | 36 | 15 |
| (16) Cormier | 49 | 49 | 45 | 14 | 24 | 81 | 39 | 8 | -[5] | - | 47 | 6 | 43 | 12 |
| (17) Bass | 92 | 21 | 40 | 29 | 24 | 48 | 30[6] | 9 | 30[6] | 19 | 22 | 10 | - | - |
| (18) Lantinga | 24 | 24 | 8 | 0 | - | - | -[7] | - | -[8] | - | -[9] | - | - | - |
| (19) Herrmann | 28[10] | 28 | 54 | 18 | 39 | 69 | -[11] | - | 29 | 0 | - | - | - | - |
| (20) Alexander | 28 | 30 | 0 | 0 | - | - | 25 | 3 | 4 | 3 | 50 | 10 | - | - |

[1] Rounded figures; do not always add up to 100%
[2] The groups did not differ significantly in terms of current or at least one past major depression
[3] patients with CAD and panic disorder scored significantly lower on the ZUNG anxiety scale than the patient with NCA without panic disorder.
[4] Patients in the NCA group had significantly higher [$p < .03$] anxiety scores than patients in the CAD group.
[5] Patients in the NCA group had significantly higher [$p < .05$] anxiety scores on the Zung Anxiety Scale than patients in the CAD group.
[6] Anxiety or Depression score > 10 on Hospital Anxiety Depression Scale
[7] Patients in the NCA group scored significantly higher than CAD patients on the Beck Depression Inventory [$p < 0.007$]
[8] Patients in the NCA group scored significantly higher than CAD patients on the State Trait Inventory Scale and Millon Somatic Anxiety [$p < 0.007$] for each
[9] Patients in the NCA group significantly mentioned a larger number of panic symptoms than patients in the CAD group [$p < 0.007$]
[10] Of a total group of 203 patients, 60 were angiographically tested
[11] No significant difference between NCA and CAD

Hyperventilation (hypocapnia) is also raised as a possible cause for the perceived chest pain with normal coronary arteries. Bass and associates (29) reported 74% of their group I patients having Unexplained Breathing Disorder (UBD) compared to 47% in group II and 13% in group III. Furthermore, in their 1988 study, Bass and associates (17), found an important association between mood disturbance and hypocapnia. Almost half of the patients with elevated anxiety and depression were hypocapnic at rest. Hoes and colleagues (35) emphasized the relationship between hyperventilation and panic disorder.

In their group of 274 patients, 35% of the patients with hyperventilation and only 5% of the non-hyperventilating patients showed panic disorder. Moreyra and colleagues (36) noted that in their study of 40 patients with chest pain, but angiographically normal arteries, 91% of the women and 66% of the men suffered from hyperventilation.

From the psychological perspective, Beunderman and Duyvis (37) propose an affective-cognitive view regarding cardiac phobia. In their model they emphasize that the relation between physical complaints and fear of cardiac problems is established and maintained by processes, such as:

1. *Labelling*. Whenever a patient senses a pain in the chest it is attributed to an approaching heart attack. This label then is a source of fear, which in turn provokes a physical phenomenon.
2. *Anticipating*. Even when a patient does not have any complaints, complaints may be anticipated, which could itself provoke a feeling of anxiety. Any feelings induced by this anticipation could be labelled as cardiac complaints.
3. *Attention*. Labelling and anticipation may increasingly direct the patient's attention towards specific parts of the body. As a result the level of perception is decreased, and all kinds of sensations become perceptible. These sensations are then labelled as cardiac complaints. The relation can be maintained or strengthened by hyperventilation.

Eifert (23) proposed an behavioural-cognitive model which encompasses, in addition to biological influences, several factors derived from previous and present learning experiences. Present learning processes emphasize the reinforcing characteristics of the consequences of pain behaviour, such as compulsive help seeking, avoiding leisure and work activities, excessive use of medical facilities.

Regarding previous learning processes, Eifert (23) suggests that separation anxiety might be a contributing factor for cardiac phobia. This view is supported by his interview study with 20 cardiophobics. Eighty percent of these patients had experienced some form of serious separation from a significant person before their first episode of chest pain. Forty-five percent had experienced the death of a significant person in childhood, and in all but one case deaths were caused by heart conditions. Furthermore, 35% of the patients reported to have been physically or sexually abused and 15% to have been left behind by their mother.

Erdman (38) used a psycho-dynamic model to explain cardiac phobia. He states that two independent processes are at the basis of this. The first process concerns pursuits/goals which a person wants to achieve. These pursuits can, however evoke feelings of anxiety. Because of this, they have to be suppressed, as nobody wants to sense anxiety. But as the need increases to yield to the pursuits, so does the feeling of anxiety. Anxiety is accompanied by a feeling of guilt when the pursuits are prohibited by conscience. When these feelings of guilt reach a certain height, a desire for punishment arises; punishing oneself (e.g. by thoughts about death caused by cardiac problems) in advance could alleviate the hideous feeling of guilt (see e.g. Pilowsky (39)).

The second process concerns the development from a dependent baby to an independent adult, also called the individuation process. Problems with parent-separation can lead to intrapsychic conflicts accompanied by feelings of hostility against parents and possible feelings of guilt. Successful individuation is only achieved when certain bothering conscience-feelings can be set aside. If one is not successful in achieving this, feelings of guilt will prevail, again possibly leading to a desire for punishment. Of course one should note that these processes are realized on an unconscious level.

## 2.5 Predictability

In 1985, Channer and colleagues (12), conducted a study among 87 consecutive patients with chest pain by measuring anxiety and depression before diagnostic exercise treadmill testing. Anxiety and depression scores were acquired by means of the Hospital Anxiety Depression (HAD) self-assessment questionnaire (40). Their main conclusions were that patients with high scores of anxiety and depression, had negative exercise tests. The study also showed that relatively more women had negative exercise tests. Furthermore, anxiety and depression were more common in females. As far as chest pain is concerned, more patients with negative exercise test were judged to have atypical chest pain and significantly more patients with atypical chest pain had high anxiety scores. With the aid of discriminant analysis a predictive probability was obtained. The probability of a negative exercise test in males who were both anxious and depressed and had atypical chest pain was 97% and in females 99%.

In 1989, Kushner (41) studied a group of 187 patients who were suffering from atypical chest pain and had no evidence of CAD. By means of cross-validation, a predictive ability was assessed for panic disorder. It appeared that the score on a Zung Self-Rating Anxiety Scale (SAS) and the subjects' age contributed significantly to the predictive power of the discriminant function equation. Seventy percent of the cases were correctly classified using a predictive equation based on the SAS score alone. Kushner (41) concluded that "... the current findings suggest that a predictive equation using the SAS alone, or in conjunction with minimal demographic information, can aid substantially in the identification of individuals presenting to cardiologists with atypical chest pain who are negative for CAD but who may be suffering from panic disorder" (41).

## 2.6 Follow-up studies

What happens to the patients after they have undergone the strenuous diagnostic exercise or angiographic testing? One would like to think that a negative test would reassure patients and they would decline from having further complaints. A vast amount of the literature, however, shows that such is not the case, even though the prospects of survival for this group of patients are high (13, 18, 21, 42-52).

Ockene and co-workers studied a group of 57 patients with entirely normal results on coronary arteriography. In a follow-up study after an average of 16 months, none of the patients had died or experienced myocardial infarction. However, 70% of the patients still complained of chest pain, 12% of them even said their pain had become worse and many remained limited in their daily activities (44). Similar results were found by Pasternak et al. (43) (also see Table 2.2).

In a study of patients with normal or minimally diseased coronary arteries by Wielgosz and associates (48), three cardiac deaths were found in the year following angiography. Of the 548 patients 181 (33%) became pain free, two-hundred and fifteen (39%) patients had less pain, but a large number (28%) continued to have similar or worse chest pain (Table 2.2). Unimproved chest pain was chiefly found to be related to the female sex and atypical chest pain.

**Table 2.2** *Follow-up studies of patient with Normal or near normal Coronary Arteries.*

| Ref | First author | N | average follow-up period(yr) | Pain complaints (%)[1] | | |
|---|---|---|---|---|---|---|
| | | | | none or less | same | worse |
| (44) | Ockene | 57 | 1.3 | 42 | 46 | 12 |
| (43) | Pasternak | 159 | 3.6 | 53 | 30 | 8[2] |
| (46) | Isner | 121 | 4.3 | 30 | 60 | 10 |
| (36) | Moreyra | 40 | 2.0 | 83 | 18 | 0 |
| (47) | Bass | 46 | 1.0 | 59 | 33 | 9 |
| (48) | Wielgosz | 548 | 1.0 | 72 | 26 | 2 |
| (13) | Papanicalaou | 1977 | 6.3 | -[3] | 70[3] | -[3] |
| (50) | Van Dorpe | 142 | 4.1 | 65 | 20 | 14 |
| (18) | Lantinga | 24 | 1.0 | -[4] | 71[4] | -[4] |
| (51) | Potts | 46 | 11.4 | 26[5] | 74 | - |
| (52) | Hirota | 274 | 6.2 | 83[6] | 15 | - |

[1] Rounded figures; do not always add up to 100%

[2] Figures show the **frequency** of attacks of chest pain (10% is unsure about frequency)

[3] 70 percent of the patients complained of continuing chest discomfort at follow up; severity is not specified.

[4] 86 percent of the patients with normal coronary arteries continued to experience chest pain at least once a week, 71% reported that their pain was unchanged or worse, 63% were still under a physician's care for chest pain symptoms.

[5] Only 26% of the patients had **no** chest pain in the six months preceding the interview, 74% still reported chest pain, either less, the same or worse.

[6] 83.3% of the patients were free from chest pain for at least 1 year. 15% continued to complain of chest pains of various intensity

Bass (47) conducted a follow-up study of the 46 patients who had no or slight coronary artery disease, twelve months after the initial angiography. Nineteen (42%) patients continued to complain of chest pain one year after angiography. These patients had a significantly higher psychiatric morbidity and neuroticism scores at the initial assessment than those whose chest pain had lessened. Similar chest pain figures were found by Potts and Bass (51) after an average follow-up period of 11.4 years.

Lantinga's study (18) showed that 1 year after catherization of the patients with normal coronary arteries 86 percent continued to experience chest pain at least once a week, 71% reported that their pain was unchanged or worse, while 63% were still under a physician's care for chest pain symptoms.

Contrary to the findings mentioned, Hirota (52), however, showed that in Japan only a small number (15%) of NCA patients continued to suffer from chest pain after a follow-up period varying from 2 to 13 years.

## 2.7 Treatment

Next to medical treatment with for instance imipramine (53), non-cardiac chest pain can often be treated successfully by means of psychotherapy. Klimes and co-workers (54) treated patients successfully with a maximum of 11 cognitive-behavioural treatment sessions. They randomly allocated their patients to either a cognitive-behavioural treatment (CBT) or to an assessment-only control (AOC) group. In their treatment they emphasized that while the pain was "real", it was not necessarily caused by serious organic pathology. Patients were taught how to anticipate and control pain. In the therapy sessions patients were introduced to progressive muscle relaxation, distraction strategies and monitoring of the relationship of chest pain to mood and activity. The patients in the CBT-group improved significantly, compared to the AOC-group, on measures such as days free of pain, psychological distress, avoidance of activity due to pain and on depressed mood. In the AOC group none of the patients improved on these measurements. They too were offered the same treatment as the CBT-group, after which their symptoms diminished. At follow-up after 4-6 months, there was a non-significant trend for patients' chest pain and its limiting effect to continue to improve.

Nutzinger and colleagues (55) were also successful in treating patients with cardiac phobia by means of a behaviour therapy program. However, a lower educational level, being single, and interpersonal difficulties and conflicts were factors associated with a poor prognosis.

A hypothetical model for cognitive treatment is described by Salkovskis (56). In this treatment model a link between non-cardiac chest pain and panic attacks is made. Misinterpretations of chest pain and the associated anxiety play a central role. These misinterpretations (so-called "catastrophing thoughts") are identified during the treatment. Verbal techniques and behavioural experiments are used to "decatastrophize" the explanations of anxiety symptoms. Verbal techniques include discussions which direct the patient to less threatening interpretations. The behavioural experiments include a hyperventilation provocation test, during which many patients begin to experience chest pain. By

learning simple breathing techniques patients are enabled to control their breathing during panic attacks. Patients who believe their symptoms to be too strong to be of a psychological nature, are exposed to a list of paired words which represent symptoms and related catastrophes (e.g. chest tight -- heart attack). Three fourths of the patients then experience symptoms of panic.

A similar hypothetical treatment model is suggested by Beunderman and Duyvis (37). As mentioned earlier, the relation between the physical complaints and cardiac phobia are initiated and maintained by three cognitive processes; labelling, anticipation and attention. The model of treatment is a step-by-step approach. The first step particularly focuses on the physical complaints. The main objective is to break through the circular process by changing the cognitions and tackling the hyperventilation. To achieve this the patient receives extensive information about the relation between fear, respiration and hyperventilation. A hyperventilation provocation test as well as respiratory exercises enhances the patient's insight into the circular process. The second step focuses on the patient's avoidance behaviour. Also progressive relaxation is taught. In the third step the patient, with the help of a therapist learns how to differentiate further between psychological factors enhancing the complaints.

Concluding we come to the following suggestions for the treatment of cardiac phobia.

## 2.8 Recommendations and conclusions

Angiographic and, to a lesser extent treadmill testing (16) can provide evidence for coronary insufficiencies. Even though cardiac or other causes for the complaints have been ruled out, many patients do still not feel reassured about the origin of their complaints (44, 47-49, 57). These patients may profit from psychological help.

Various methods can be applied in the treatment of cardiac phobia. Taking the nature and seriousness into account the following methods or combinations may be applied.

- Exposure to internal stimuli which generally provoke the pain and anxiety
- Cognitive relabelling of the chest pain
- Relaxation training (with or without EMG-feedback)
- Breathing exercises

- Insight oriented psychotherapy related to separation conflicts and/or the dependency problems
- Psychopharmalogical treatment for depression and anxiety problems

In conclusion, as Eifert (23) suggests, cardiac phobia should be considered as a phobic anxiety disorder rather than as a "non-organic" chest pain problem. Early recognition of cardiac phobia is important, since the prognosis tend to get worse if patients stay in the medical circuit (somatic fixation). Apart from cardiac phobia, it would be of interest to further study the role of anxiety, depression, hyperventilation and panic disorder in patients with proven coronary artery disease, in order to gain insight into the relationship between CAD and psychic symptoms in an early stage.

## 2.9 References

1. Paul O. Da Costa's syndrome or neurocirculatory asthenia (Review). Brit Heart J 1987; 58(4):306-315.
2. Hartstone H. On heart disease in the army. Am J Med Sci 1864; 48:89-92.
3. Stillé A. Address before the Philadelphia Country Medical Society. Philadelphia: Collins, Printer, 1863: 18-19.
4. Maclean WC. Diseases of the heart in the British Army: the cause and remedy. Brit Med J 1867;i :161-164.
5. Da Costa JM. On irritable heart: a clinical study of a form of functional cardiac disorder and its consequences. Am J Med Sci 1871; 61(121): 17-52.
6. Lewis T. The soldier's heart and the effort syndrome.New York: Paul B. Hoeber, 1919:1-103.
7. Levine SA. The origin of the term neurocirculatory asthenia. N Eng J Med 1965; 273: 604-605.
8. Kannel WB, Dawber TR, Cohen ME. The electrocardiogram in neurocirculatory astenia (anxiety, neurosis or neurasthenia): a study of 203 neurocirculatory asthenia patients and 757 healthy controls in the Framingham study. Ann Intern Med 1958;49:1351-1360.
9. Fava GA, Magelli C, Savron G, et al. Neurocirculatory asthenia: a reassessment using modern psychosomatic criteria. Acta Psychiatr Scand 1994; 89(5): 314-319.
10. Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med. 1984;14(1):51-61.

11. Costa PT, Zonderman AB, Engel BT, Baile WF, Brimlow DL, Brinker J. The relation of chest pain symptoms to angiographic findings of coronary artery stenosis and neuroticism. Psychosom Med. 1985;47(3):285-293.
12. Channer KS, Papouchado M, James MA, Rees JR. Anxiety and depression in patients with chest pain referred for exercise testing. Lancet 1985; 2(8459): 820-823.
13. Papanicolaou MN, Califf RM, Hlatky MA, et al. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. Am J Cardiol 1986;58(13):1181-1187.
14. Beitman BD, Basha I, Flaker G, DeRosear L, Mukerji V, Lamberti JW. Major depression in cardiology chest pain patients without coronary artery disease and with panic disorder. J Affective Disord 1987;13(1):51-59.
15. Katon W, Hall ML, Russo J, et al. Chest pain: relationship of psychiatric illness to coronary arteriographic results. Am J Med 1988;84(1):1-9.
16. Cormier LE, Katon W, Russo J, Hollifield M, Hall ML, Vitaliano PP. Chest pain with negative cardiac diagnostic studies. Relationship to psychiatric illness. J Nerv Ment Dis 1988;176(6):351-358.
17. Bass C, Chambers JB, Kiff P, Cooper D, Gardner WN. Panic anxiety and hyperventilation in patients with chest pain: a controlled study. Q J Med 1988; 69(260): 949-959.
18. Lantinga LJ, Sprafkin RP, McCroskery JH, Baker MT, Warner RA, Hill NE. One-year psychosocial follow-up of patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1988;62(4): 209-213.
19. Herrmann C, Scholz KH, Kreuzer H. [Psychologic screening of patients of a cardiologic acute care clinic with the German version of the Hospital Anxiety and Depression Scale] Psychologisches Screening von Patienten einer kardiologischen Akutklinik mt einer deutchen Fassung der "Hospital Anxiety and Depression" (HAD)-Skala. Psychother Psychosom Med Psychol. 1991;41(2):83-92.
20. Alexander PJ, Prabhu SG, Krishnamoorthy ES, Halkatti PC. Mental disorders in patients with noncardiac chest pain. Acta Psychiatr Scan 1994; 89(5): 291-293.
21. Mayou R, Bryant B, Forfar C, Clark D. Non-cardiac chest pain and benign palpitations in the cardiac clinic. Br Heart J 1994;72:548-553.
22. Faxon DP, McCabe CH, Kreigel DE, Ryan TJ. Therapeutic and economic value of a normal coronary angiogram. Am J Med 1982;73:500-505.
23. Eifert GH. Cardiophobia: a paradigmatic behavioural model of heart-focused anxiety and non-anginal chest pain. Behav Res Ther 1992; 30(4): 329-345.
24. Katon W. Panic disorder and somatisation: Review of 55 cases. Am J Med 1984; 77:101-106.

25. Beitman BD, Basha I, Flaker G, et al. Atypical or nonanginal chest pain. Panic disorder or coronary artery disease? Arch Intern Med 1987; 147(9): 1548-1552.
26. Beitman BD, Mukerji V, Lamberti JW, et al. Panic disorder in patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1989;63(18):1399-1403.
27. APA. Diagnostic and statistical manual of mental disorders, 3rd ed. Revised.Washington DC: APA, 1987
28. Waxler EB, Kimbris D, Dreifus LS. The fate of women with normal coronary arteriograms and chest pain resembling angina pectoris. Am J Cardiol 1971;28:25-32.
29. Bass C, Cawley R, Wade C, et al. Unexplained breathlessness and psychiatric morbidity in patients with normal and abnormal coronary arteries. Lancet. 1983;1(8325):605-609.
30. Gasic S, Grünberger J, Korn A, Oberhummer I, Zapotoczky HG. Biochemical, physical and psychological findings in patients suffering from cardiac neurosis. Neuropsychobiology 1985;13(1-2):12-16.
31. Cannon RO3, Leon MB, Watson RM, Rosing DR, Epstein SE. Chest pain and "normal" coronary arteries--role of small coronary arteries. Am J Cardiol 1985;55(3):50.
32. Cannon RO3, Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. Am J Cardiol 1988; 61(15): 1338-1343.
33. Katon W. Chest pain, cardiac disease and panic disorder. J Clin Psychiatry 1990; 51(5): 27-30.
34. Davies HA. Anginal pain of esophageal origin: clinical presentation, prevalence, and prognosis. Am J Med 1992;92(5A):5.
35. Hoes MJAJM, Colla P, Van Doorn P, Folgering H, De Swart J. Hyperventilation and panic attacks. J Clin Psychiatry 1987;48:435-437.
36. Moreyra AE, McGough WE, Hosler M, Kostis JB. Clinical improvement of patients with chest pain and normal coronary arteries after coronary arteriography: The possible role of hyperventilation syndrome. Int J Cardiol 1982;2:306-308.
37. Beunderman R, Duyvis BJ. Cardiac Phobia. In: Kaptein AA, Ploeg HMvd, Garssens B, Scheurs PJG, Beunderman R, ed. Behavioural Medicine. Chichester: John Wiley & Sons, 1990: 95-107.
38. Erdman RAM. [What is cardiac neurosis?] Wat is een hartneurose? Hart Bull 1992;23:127-129.
39. Pilowsky I. Psychodynamic aspects of the pain experience. In: Sternbach RA, ed. The psychology of pain. New York: Raven Press, 1978: 203-217.
40. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-370.

41. Kushner MG, Beitman BD, Beck NC. Factors predictive of panic disorder in cardiology patients with chest pain and no evidence of coronary artery disease: a cross-validation. J Psychosom Res 1989;33(2):207-215.
42. Proudfit WL, Bruschke AVG, Sones FM Jr. Clinical course of patients with normal or slightly or moderately abnormal coronary arteriograms: 10-year follow-up of 521 patients. Circulation 1980;62:712-717.
43. Pasternak RC, Thibault GE, Savoia M, DeSanctis RW, Hutter AM. Chest pain with angiographically insignificant coronary arterial obstruction. Clinical presentation and long-term follow-up. Am J Med 1980; 68: 813-817.
44. Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary arteriograms: A follow-up study of functional status. N Eng J Med 1980;303:1249-1252.
45. Wilcox RG, Roland JM, Hampton JR. Prognosis of patients with "chest pain ?cause". Br Med J 1981;282:431-433.
46. Isner JM, Salem DN, Banas JS Jr., Levine HJ. Long-term clinical course of patients with normal coronary arteriography: Follow-up study of 121 patients with normal or nearly normal coronary arteriograms. Am Heart J 1981; 102: 645-653.
47. Bass C, Wade C, Hand D, Jackson G. Patients with angina with normal and near normal coronary arteries: clinical and psychosocial state 12 months after angiography. Br Med J Clin Res Ed. 1983;287(6404): 1505-1508.
48. Wielgosz AT, Fletcher RH, McCants CB, McKinnis RA, Haney TL, Williams RB. Unimproved chest pain in patients with minimal or no coronary disease: a behavioral phenomenon. Am Heart J 1984;108(1):67-72.
49. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. J Am Coll Cardiol 1986;7(3):479-483.
50. Van Dorpe A, Piessens J, Willems JL, De Geest H. Unexplained chest pain with normal coronary arteriograms. A follow-up study. Cardiology. 1987; 74(6): 436-443.
51. Potts SG, Bass CM. Psychosocial outcome and use of medical resources in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. Q J Med 1993;86(9):583-593.
52. Hirota Y, Ohnaka H, Tsuji R, et al. Excellent prognosis of Japanese patients with chest pain and normal or nearly normal coronary arteries--2- to 13-year follow-up of 274 patients after coronary cineangiography. Jpn Circ J 1994;58(1):43-48.
53. Cannon R3, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms [see comments]. N Eng J Med 1994;330(20):1411-1417.

54. Klimes I, Mayou RA, Pearce MJ, Coles L, Fagg JR. Psychological treatment for atypical non-cardiac chest pain: A controlled evaluation. Psychol Med 1990;20(3):605-611.
55. Nutzinger DO, Cayiroglu S, Grünberger J, Kieffer W, Zapotczky HG. Prognosis of cardiac phobia. Psychopathology 1990;23:63-72.
56. Salkovskis PM. Psychological treatment of noncardiac chest pain: the cognitive approach. Am J Med. 1992;92(5A):114.
57. Channer KS, James MA, Papouchado M, Rees JR. Failure of a negative exercise test to reassure patients with chest pain. Q J Med 1987; 63(240): 315-322.

# 3. Empirical psychological modelling of chest pain; a comparative study

*A.W. Serlie, H.J. Duivenvoorden, J. Passchier, F.J. ten Cate, J.W. Deckers, R.A.M. Erdman*

*(Journal of Psychosomatic Research: in press)*

## 3.1 Abstract

In retrospective this study the psychological profiles of 67 non-cardiac patients (NCA) and 47 patients with coronary artery disease (CAD) were analyzed, in order to construct an empirical-psychological model which would be able to discriminate these two groups. All patients were suffering from chest pain at the time of referral by their general practitioner. The Non-cardiac patients were significantly younger, more often female, single and non-smokers. The two groups differed significantly on anxiety, somatisation, obsessive compulsive behaviour, psychoneuroticism and hyperventilation. Logistic regression analysis on the variables jointly, showed that age, gender, anxiety and hyperventilation contributed significantly to the model for discriminating between both groups. Crossvalidation showed that the constructed model was stable.

## 3.2 Introduction

Over the past years a considerable amount of research has been conducted on the relationship between chest pain with normal coronary arteries and psychological dysfunctioning (1). Recent studies have shown that up to one third of the patients with chest pain undergoing cardiac catherization or treadmill testing have normal or minimally diseased coronary arteries (NCA) (2-13). These patients are relatively young, female, suffer from panic disorder, hyperventilate, are considered depressed and anxious and have a higher prevalence of

atypical chest pain. Frequently these patients are classified as cardiac phobics (2, 4, 6-8).

Although the prospects of survival for these patients are favourable (5, 10, 14-22), patients' symptoms do tend persist or even increase over the years. Ockene's study (16), for instance, showed that after an average follow-up period of 16 months, 70% of the patients with normal coronary angiograms, still complained of chest pain. Twelve percent of them indicated that their chest pain had even become worse during follow-up and many remained limited in their daily activities. Similarly in a study by Wielgosz (20) of 548 non-cardiac chest pain patients, 33% became pain free, 39% had less pain, but 28% continued to have similar or worse chest pain, whereas only three cardiac deaths occurred in the year following angiography.

It may be concluded that the present medical approach towards non-cardiac patients does apparently not suffice, and medical consumption and, as a consequence, costs remain high (23).

All of the studies mentioned above only signal the differences between the two groups of chest pain patients, but do not quantitatively relate them to a model in which the variables with differential potential are entered, thereby allowing for a quicker diagnosis and a more tailored treatment. In the present study we will make an effort to fill this gap. Objective of this study was to construct a practical statistical model based on demographic and psychological variables, which can, in an early stage, quantitatively discriminate between chest pain patients with diseased coronary arteries and patients with non-cardiac chest pain.

## 3.3 Methods

### 3.3.1 Patients

Eligible for this study were patients who had been referred to the cardiology out-patient's clinic of the Rotterdam University Hospital, for the first time, from March 1991 up to January 1993, with chest pain as a chief complaint. Exclusion criteria were insufficient proficiency of the Dutch language, age younger than 18 or older than 75 years and a history of psychiatric illness. Furthermore, it was also made sure that no further medical complications, such

as myocardial infarction or by-pass surgery, had occurred during the time of referral and the onset on the study.

Patients meeting these criteria were selected from medical records available at the Thoraxcentre of the Rotterdam University Hospital. All selected patients had undergone standard cardiological testing in order to assess whether the chest pain was of a somatic nature. In the next step all medical records were checked by an experienced cardiologist, to make sure that the patient's complaints were either cardiac or non-cardiac.

In total 163 patients were eligible for this study, 96 in the non-cardiac group (NCA) and 67 in the group with coronary artery disease (CAD). After elimination of patients unwilling to participate ($n_{nca}=26$; $n_{cad}=15$) and inconclusive data ($n_{nca}=3$; $n_{cad}=5$) a total of 67 non-cardiac patients (29 men, 38 women; mean age 48.5 yrs, SD 12.0) and 47 cardiac patients (36 men, 11 women; mean age 60.7 yrs, SD 9.0) were used for statistical analysis.

### 3.3.2 Procedure

Patients were sent a letter by the research group, informing them about the study. After one week they were phoned to make an appointment at the cardiology out-patient's clinic, to fill out psychological questionnaires. These appointments were generally one week later. The patients were allowed to take there time in completing the questionnaires, but usually this took no longer than one hour.

### 3.3.3 Psychological assessment

On the basis of earlier findings (2-11), psychological characteristics were measured with the following questionnaires, representing the constructs of relevance.

The Hospital Anxiety Depression Scale (HAD) (24), was used to assess anxiety and depression. The questionnaire consists of 14 questions, half reflecting anxiety and half depression. The answer possibilities, indicate the intensity of the given mood; the sum of the individual scores give an overall anxiety (min 0; max 21) and depression (min 0; max 21) score. Validity and reliability have been proven for British studies (4).

Psychopathology was measured with the General Health Questionnaire (GHQ-12). The twelve items of this self-rating questionnaire reflect a measure of

severity of functional non-psychotic psychopathology. The questions relate to unusual or unpleasant psychological experiences. Patients are requested to answer by indicating, on a four point scale, the difference between their present situation compared to their normal situation, choosing from 'none', 'no more than usual', 'more than usual' and 'a lot more than usual'. The total scores (min 0; max 12) were obtained using the conventional scoring (0-0-1-1) (25). Validity and reliability for the Dutch version have been demonstrated (26, 27).

The Symptom Checklist (SCL-90) (28) was used to assess agoraphobia (min 7; max 35; $\bar{x}_{norm}$ 8.4), anxiety (min 10; max 50; $\bar{x}_{norm}$ 13.9), depression (min 16; max 80; $\bar{x}_{norm}$ 22.5), somatisation (min 12; max 60; $\bar{x}_{norm}$ 17.8), obsessive compulsive behaviour (min 9; max 45; $\bar{x}_{norm}$ 13.7), interpersonal sensitivity (min 18; max 90; $\bar{x}_{norm}$ 25.6), hostility (min 6; max 30; $\bar{x}_{norm}$ 7.6), sleeping-problems (min 3; max 15; $\bar{x}_{norm}$ 4.9) and the total of all subscales, including the residual items; psychoneuroticism (min 90; max 450; $\bar{x}_{norm}$ 123.9). The SCL-90 is a widely used self-report questionnaire in medical research, to categorize and quantify psychological distress. Patients rate on a five-point Likert scale (1 = not at all, 5 = extremely) the degree of distress they have experienced in the preceding week, from each of 90 items. Validity and reliability have proven to be good for the Dutch population (29).

Hyperventilation was measured with the Nijmegen Questionnaire (NQ) (30). The questionnaire consists of 16 complaints whose frequency of incidence can be indicated on a five-point Likert scale (never, rarely, sometimes, often and very frequently). The complaints relate to different systems; (a) cardiovascular e.g. 'palpitations'; (b) neurological, e.g. 'dizzy spells', tingling fingers'; (c) respiratory e.g. 'shortness of breath'; (d) gastrointestinal, e.g. bloated abdominal sensation'; (e) psyche, e.g. 'tense' and 'anxious feeling'. Total scores can range from 0 to 64, whereby 0-20 is considered as probably no hyperventilation, 20-30 further observation needed and more than 30 most certainly hyperventilation. In Van Dixhoorn and Duivenvoorden's study (30) the sensitivity of the Nijmegen Questionnaire in relation to the clinical diagnosis was 91% and the specificity 95%.

Hypochondria was assessed with the Maastricht hypochondria scale (MEGAH) (31). Sixty-seven statements are divided into 5 subscales; 'fear of own health' (min 12; max 60; < 40: hypochondriac fears of own health), 'general health fear' (min 16; max 80; < 40: hypochondriac general health fears), 'illness

belief' (min 7; max 35; < 28: hypochondriac illness belief), 'confidence in doctors' (min 6; max 30) and 'search of medical information' (min 3; max 15). The sum of the first three subscales is a measure for the amount of hypochondria (min 35; max 175; < 100: hypochondria according to DSM-III-R). The statements have to be answered on a five-point scale varying from 1; 'strongly agree' to 5; 'strongly disagree', whereby a lower score is less favourable.

Displeasure (min 10; max 30) and disability (min 12; max 36) were assessed with subscales of the Heart Patients Psychological Questionnaire (HPPQ) (32). The subscales consist of respectively 10 and 12 items which can be rated on a three-point scale (yes/?/no). Validity and reliability for the Dutch population have proven to be sufficient (29).

Two subscales of the Fear Survey Schedule (FSS) (33-35) were used to assess 'fear for bodily injury' and 'social anxiety'. The subscales consist of respectively 12 and 13 items which have to be rated on a five-point Likert scale (1 = not at all, 5 = extremely). Validity and reliability for the Dutch population have proven to be good.

State and trait anxiety were assessed by means of the State Trait Anxiety Inventory (STAI) (36). Each subscale entails 20 items. Items are scored on a four-point Likert scale (state: 1 = not at all, 4 = very much; trait: 1 = almost never, 4 = almost always). Reliability of this questionnaire has proven to be good, for the Dutch population (29).

By means of the Profile Of Mood States (POMS) (37) depression, anger, fatigue, vigour and tension were measured. The subscales consist of respectively 8, 7, 6, 5 and 6 items which have to be rated on a 5-point Likert scale varying from 0 = not at all to 4 = extremely. Each item reflects a state of mood which might have occurred during the preceding days. The total score of all items gives an indication of the patient's peevishness. Reliability in the Netherlands, has proven to be good (37).

The Maastricht Questionnaire (MQ) (38) was used to measure vital exhaustion. This self-report questionnaire consists of 21 items which can be rated on a three-point scale (yes/?/no). The total score can range from 0 to 42. Validity and reliability has been demonstrated (38)

### 3.3.4 Statistical analysis

Before answering the research questions, missing data were estimated for variables of which the percentage missing was below 15%. If the percentage missing was larger than 15% the variable was removed from analysis. For estimating the values of the missing data the predicted mean matching method was used (39). Other variables were utilised as predictors for the missing variables. Regression analysis, with the procedure backwards elimination, was used for this purpose. Only predictor variables that were significant at 0.05 level were maintained in the regression model.

For the psychological variables the means including the 95% confidence intervals and the 95% confidence intervals for the difference were calculated. The statistical significance is defined as whether the 95% confidence interval of the difference includes the value 0.0 or not (40). In addition the magnitude of the difference between the two groups of patients is calculated using Cohen's $\delta$ (41).

Furthermore, all psychological variables, age and gender were examined by means of a logistic regression analysis. With this multivariate modelling an estimation of the probability of an event (cardiac or non-cardiac) occurring can be made. Standardised scores of the variables were used in the analyses, in order to be able to more easily compare estimated coefficients ($\beta$). In the analyses the backward elimination procedure was used. Here too, only predictor variables that were significant at 0.05 level were maintained in the model.

The remaining variables were consequently put into a second logistic regression analysis to be able to adjust the model for age and gender. This was done by calculating the predicted probability using the same estimation coefficients for the psychological variables, but setting them to zero for age and gender.

Thereafter, a receiver-operator characteristic (ROC) curve was constructed for data adjusted for age and gender. The logistic model calculated the predicted probability of being a non-cardiac patient for all subjects and subsequently sensitivity and specificity were calculated. In the ROC curve, the true-positive rate (sensitivity) is plotted against the false-positive rate (1 minus specificity) and the discriminative ability of a test is shown by the position of

the full curve: the farther upward and to the left the curve lies in the figure, the more optimal the test. Thus, the area under the ROC-curve reflects the performance of the model, in a sense that a larger surface area reflects a higher performance (42).

Finally, the model was crossvalidated by randomly assigning patients into five strata, making sure that each stratum contained the same proportion of non-cardiac/cardiac and male/female patients as the total group. A model was constructed based on four of these strata and the probabilities of the fifth stratum were then estimated based on the constructed model. This procedure was repeated five times, for each combination. Consequently, the estimated probabilities were tested against the probabilities of the model based on all patients, using a regression analysis.

**Table 3.1** *Demographic characteristics of non-cardiac and cardiac patients*

| | NCA (n=67) | CAD (n=47) | P value |
|---|---|---|---|
| Age (mean (SD)) | 48.49 (12.02) | 60.65 (9.02) | $\ll 0.01$ |
| Gender (male:female) | 29:38 | 36:11 | $\ll 0.01$[a] |
| Marital status (partner:single) | 45:22 | 43:4 | $<0.05$[b] |
| Full time employment (yes:no) | 22:45 | 14:33 | 0.89 |
| Smoking (yes:no:never) | 15:23:29 | 12:27:8 | $<0.01$[c] |

[a] $\chi^2 = 11.19$ df=1
[b] $\chi^2 = 7.95$ df=1
[c] $\chi^2 = 9.79$ df=2

All data were analyzed using the SPSS/PC programme (43).

### 3.4 Results

Table 3.1 shows the general characteristics of the two patient groups. Consistent with findings in earlier studies (2-11), the non-cardiac patients were significantly younger (95% $CI_{diff}$; -16.29 to -8.01), more often female ($p \ll 0.01$), single ($p < 0.05$) and a larger proportion had never smoked ($p < 0.01$).

In Table 3.2 the psychological characteristics for both groups can be found. As can be seen there is a significant difference between the two groups for HAD-anxiety (95% $CI_{diff}$; 0.23 to 3.35), SCL-anxiety (95% $CI_{diff}$; 1.23 to 5.83), Somatisation (95% $CI_{diff}$ ; 1.38 to 7.34), obsessive compulsive behaviour (95%

**Table 3.2** *Psychological Characteristics of non-cardiac vs cardiac patients*

| Determinant | Non-cardiac | | Cardiac | | Difference | |
|---|---|---|---|---|---|---|
| | $\bar{x}$ | 95% CI | $\bar{x}$ | 95% CI | Cohen $\delta$ | 95% CI |
| **HAD** | | | | | | |
| Anxiety | 7.61 | 6.55 ; 8.67 | 5.82 | 4.72 ; 6.92 | 0.43 | 0.23 ; 3.35 |
| Depression | 4.94 | 4.12 ; 5.76 | 4.19 | 3.25 ; 5.13 | 0.23 | -0.51 ; 2.01 |
| **GHQ** | | | | | | |
| Psychopathology | 2.97 | 2.25 ; 3.69 | 2.23 | 1.37 ; 3.09 | 0.29 | -0.24 ; 1.72 |
| **SCL-90** | | | | | | |
| Agoraphobia | 9.70 | 8.72 ; 10.68 | 8.66 | 7.76 ; 9.56 | 0.29 | -0.34 ; 2.42 |
| Anxiety | 18.32 | 16.60 ; 20.00 | 14.79 | 13.45 ; 16.13 | 0.58 | 1.23 ; 5.83 |
| Depression | 26.82 | 24.50 ; 29.18 | 23.62 | 21.42 ; 25.82 | 0.36 | -0.16 ; 6.56 |
| Somatisation | 25.32 | 23.20 ; 27.46 | 20.96 | 19.10 ; 22.82 | 0.56 | 1.38 ; 7.34 |
| Obses. compulsive | 16.20 | 14.80 ; 17.60 | 14.04 | 12.74 ; 15.34 | 0.41 | 0.16 ; 4.16 |
| Interp. sensitivity | 27.03 | 24.69 ; 29.37 | 24.67 | 22.19 ; 27.15 | 0.26 | -1.14 ; 5.86 |
| Hostility | 8.11 | 7.55 ; 8.67 | 7.63 | 6.85; 8.41 | 0.20 | -0.44 ; 1.40 |
| Sleepproblems | 6.77 | 5.87 ; 7.67 | 5.98 | 5.20; 6.76 | 0.24 | -0.47 ; 2.05 |
| Psychoneurot. | 150.73 | 140.79;160.70 | 131.92 | 122.00;141.80 | 0.49 | 4.31 ;33.31 |
| **NQ** | | | | | | |
| Hyperventilation | 22.34 | 19.70 ; 24.94 | 14.61 | 12.01 ; 17.21 | 0.78 | 3.93 ;11.53 |
| **MEGAH** | | | | | | |
| Fear own health | 48.97 | 46.79 ; 51.15 | 50.55 | 47.85 ; 53.25 | -0.17 | -5.02 ; 1.86 |
| Med. information | 10.33 | 9.43 ; 11.23 | 11.51 | 10.51 ; 12.51 | -0.33 | -2.51 ; 0.18 |
| Trust doctors | 21.67 | 20.51 ; 22.83 | 23.25 | 21.75 ; 24.75 | -0.32 | -3.46 ; 0.30 |
| Illness belief | 26.84 | 25.56 ; 28.12 | 27.11 | 25.49 ; 28.73 | -0.05 | -2.31 ; 1.77 |
| Gen. health | 39.43 | 37.29 ; 41.57 | 35.97 | 32.63 ; 39.31 | 0.35 | -0.32 ; 7.24 |
| Hypoch. index | 115.37 | 110.83;119.90 | 113.62 | 107.30;119.90 | 0.09 | -5.83 ; 9.33 |
| **HPPQ** | | | | | | |
| Disability | 23.83 | 22.21 ; 25.45 | 24.69 | 22.65 ; 26.73 | -0.13 | -3.44 ; 1.72 |
| Displeasure | 15.42 | 14.30 ; 16.54 | 14.72 | 13.38 ; 16.06 | 0.15 | -1.04 ; 2.44 |
| **FSS** | | | | | | |
| Fear bod injury | 19.72 | 18.18 ; 21.26 | 17.88 | 16.18 ; 19.58 | 0.30 | -0.48 ; 4.16 |
| Social anxiety | 21.93 | 19.61 ; 24.25 | 19.63 | 17.45 ; 21.81 | 0.26 | -1.02 ; 5.62 |
| **STAI** | | | | | | |
| State anxiety | 26.67 | 33.89 ; 39.45 | 36.98 | 34.00 ; 39.96 | -0.03 | -4.47 ; 3.85 |
| Trait anxiety | 37.64 | 35.14 ; 40.14 | 35.98 | 33.10 ; 38.86 | 0.16 | -2.18 ; 5.50 |

**Table 3.2** *continued*

| Determinant | Non-cardiac | | Cardiac | | Difference | |
|---|---|---|---|---|---|---|
| | $\bar{x}$ | 95% CI | $\bar{x}$ | 95% CI | Cohen $\delta$ | 95% CI |
| POMS | | | | | | |
| Depression | 3.46 | 2.48 ; 4.44 | 3.13 | 1.81 ; 4.45 | 0.08 | -1.27 ; 1.93 |
| Anger | 4.35 | 3.37 ; 5.33 | 3.87 | 2.27 ; 5.47 | 0.10 | -1.30 ; 2.26 |
| Fatigue | 5.94 | 4.64 ; 7.24 | 5.30 | 3.80 ; 6.80 | 0.12 | -1.36 ; 2.64 |
| Vigour | 11.44 | 10.50 ; 12.38 | 11.91 | 10.81 ; 13.01 | -0.12 | -1.93 ; 0.99 |
| Tension | 5.57 | 4.37 ; 6.77 | 4.72 | 3.50 ; 5.94 | 0.18 | -0.91 ; 2.61 |
| Total mood dist. | 28.31 | 24.41 ; 32.21 | 25.87 | 20.53 ; 31.21 | 0.14 | -4.00 ; 8.88 |
| MQ | | | | | | |
| Vit. exhaustion | 15.88 | 13.44 ; 18.32 | 13.93 | 11.11 ; 16.75 | 0.20 | -1.81 ; 5.71 |

$CI_{diff}$; 0.16 to 4.16), psychoneuroticism (95% $CI_{diff}$; 4.31 to 33.31) and hyperventilation (95% $CI_{diff}$; 3.93 to 11.53).

Using the, backward elimination, logistic regression method of analysis with the criterion variable cardiac (yes/no) and all psychological variables as the predictor variables, SCL-anxiety ($\beta$=1.40), hyperventilation ($\beta$=1.33), medical information seeking ($\beta$=-0.62), hypochondria index ($\beta$=0.58), disability ($\beta$=−0.93) and state anxiety ($\beta$=−0.77) remained in the model, giving an overall correct classification of 75.4%. Taking the priori probability of 58.8% into account the model shows an improvement of 40% ((75.4-58.8)/(100-58.8) × 100%). In order to adjust for age and gender, these variables, together with age and gender were subsequently put into a second logistic regression analysis, using the enter method. The estimation coefficients adjusted for age and gender can found in Table 3.3. Only SCL-anxiety (95% CI 1.03 to 9.81) and hyperventilation (95% CI 1.02 to 7.23) significantly contributed to the predictability of non-cardiac chest pain.

In Figure 3.1 the ROC-curve for the adjusted model is shown. The area under the adjusted ROC-curve is 0.79 (95% CI 0.70 to 0.87), indicating a high performance.

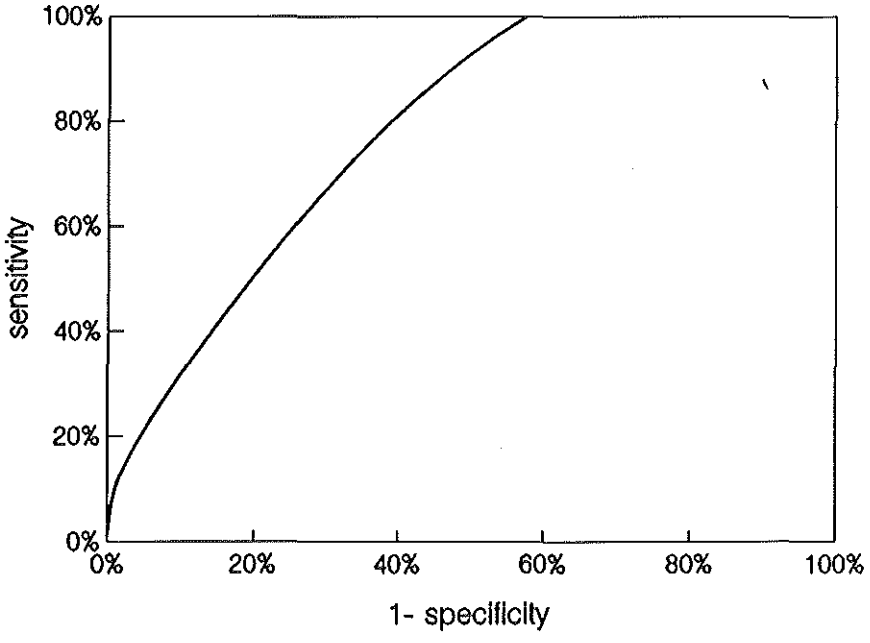
Figure 3.2 shows the predicted probability acquired by crossvalidation and the predicted probability acquired with the total model. As can be seen from the regression lines for cardiac ($\beta$= 0.97, $p \ll 0.01$) and non-cardiac ($\beta$= 0.96, $p \ll 0.01$) the model acquired by crossvalidation highly resembles the model acquired with the all the data and is therefore stable. The intersections of the

**Table 3.3** *Differential qualities for psychological determinants unadjusted and adjusted for gender and age*

| Determinant | β | | exp β | | SE | | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| | unadj | adj | unadj | adj | unadj | adj | unadjusted | adjusted |
| Anxiety SCL | 1.40 | 1.15 | 4.04 | 3.17 | 0.53 | 0.56 | 1.40 ; 11.64* | 1.03 ; 9.81* |
| Hypervent. | 1.33 | 1.00 | 2.72 | 2.72 | 0.42 | 0.49 | 1.64 ; 8.65* | 1.02 ; 7.23* |
| Med info | -0.62 | -0.30 | 0.74 | 0.74 | 0.27 | 0.31 | 0.31 ; 0.92* | 0.40 ; 1.36 |
| Hypoch. in | 0.58 | 0.62 | 1.86 | 1.86 | 0.29 | 0.34 | 1.01 ; 3.19* | 0.95 ; 3.65 |
| Disability | -0.93 | -0.44 | 0.64 | 0.64 | 0.32 | 0.36 | 0.21 ; 0.74* | 0.31 ; 1.34 |
| State anxiety | -0.77 | -1.20 | 0.30 | 0.30 | 0.34 | 0.43 | 0.25 ; 0.91* | 0.13 ; 0.71 |

* significant at 0.05 level

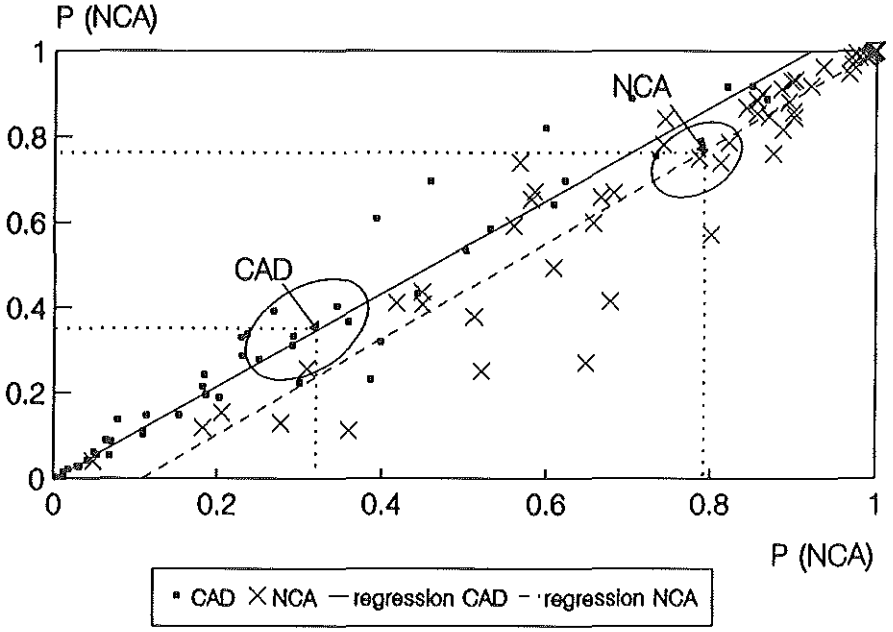
**Figure 3.1** *Receiver Operator Characteristic Curve of the model, adjusted for age and gender*




mean of the crossvalidated ($\overline{x}_{cad}$ = 0.34, $SE_{cad}$= 0.04; $\overline{x}_{nca}$ = 0.76, $SE_{cad}$= 0.03) and total model ($\overline{x}_{cad}$ = 0.30, $SE_{cad}$= 0.04; $\overline{x}_{nca}$ = 0.79, $SE_{cad}$= 0.03)

again clearly show the differentiation between non-cardiac patients and patients with coronary artery disease.

**Figure 3.2** *The probability of being a NCA patient for the total model set against the probability of being a NCA patient for the model acquired by crossvalidation.*




### 3.5 Discussion

In this study we have tried to construct an quantitative empirical-psychological model which can predict whether a patient's chest pain complaints are of a cardiac or a non-cardiac nature. Logistic regression analyses showed that, adjusted for age and gender, anxiety and hyperventilation are the foremost psychological variables that differentiate between the two groups. These findings are consistent with earlier studies (9, 44-50), in which non-cardiac patients were found to suffer significantly more from hyperventilation and anxiety disorders than cardiac patients. Moreyra and colleagues (49), for instance, found that of a group of 40 non-cardiac patients 91% of the women

and 66% of the men suffered from hyperventilation. Similarly, results from a study by Bass and colleagues (9) suggested that hyperventilation might be one important mechanism involved in the production of non-cardiac chest pain. In their study, 26% of the anxious or depressed patients suffered from hyperventilation. Almost half the patients with elevated anxiety and depression scores were hypocapnic at rest. In addition, patients with panic anxiety reported significantly more symptoms of breathlessness and other hyperventilation-related somatic complaints and developed hypocapnia on exercise more frequently than those without panic.

Additionally, however, our study has not only shown that non-cardiac patients are more anxious and suffer more from hyperventilation, but also that in addition to age and gender and questions regarding anxiety and hyperventilation, we were able to predict whether the complaints patients with chest pain were cardiac or non-cardiac, with an overall correct classification of 75.4%.

It should be clear, however, that the model constructed in this study should by no means replace diagnostic testing, but should be considered a helpful instrument, for doctors as well as patients, In our view, all standard medical diagnostic testing should be done first to exclude coronary artery disease. Only if the cardiologic tests are inconclusive, the 26 questions significantly contributing to the model should be utilized. In this way one can trace the group of patients who are anxious and hyperventilate and thus presumably are non-cardiac. Needless to say, standard diagnostic cardiologic testing regardless of gender and age is imperative. Applying the model in an early stage of diagnostic testing would most likely only enhance a policy of non-referral, which is not desirable.

Once diagnosed as non-cardiac, the patient can adequately be treated, as recent literature has shown (51-54). Hegel (54), for instance, successfully treated patients with non-cardiac chest pain due to hyperventilation. The main focus of such therapies is on relaxation and breathing exercises.

We would also recommend that further research should be conducted into the underlying characteristics of hyperventilation, such as the nature and/or origin of anxiety, but possibly also into the variables for which both patient groups appeared to be different, even though these variables did not significantly

contribute to the logistic regression model; variables such as somatisation, obsessive compulsive behaviour and psychoneuroticism.

This study has shown that our model in the form of 26 questions can adequately distinguish cardiac from non-cardiac chest pain patients. Implementation of the model, by completion of the short questionnaire, may help the treating cardiologist with the diagnosis of non-cardiac chest pain in an early stage of diagnostic testing. This would be favourable because the non-cardiac patient could be referred to a psychologist or psychiatrist more quickly for appropriate treatment, which will in turn most likely lead to a reduction of unnecessary medical consumption.

### 3.6 References

1. Serlie AW, Erdman RAM, Passchier J, Trijsburg RW, Ten Cate FJ. Psychological aspects of non-cardiac chest pain. Psychother Psychosom 1995; 64: 62-73.
2. Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med. 1984; 14(1): 51-61.
3. Costa PT, Zonderman AB, Engel BT, Baile WF, Brimlow DL, Brinker J. The relation of chest pain symptoms to angiographic findings of coronary artery stenosis and neuroticism. Psychosom Med. 1985; 47(3): 285-293.
4. Channer KS, Papouchado M, James MA, Rees JR. Anxiety and depression in patients with chest pain referred for exercise testing. Lancet 1985; 2(8459): 820-823.
5. Papanicolaou MN, Califf RM, Hlatky MA, et al. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. Am J Cardiol 1986; 58(13): 1181-1187.
6. Beitman BD, Basha I, Flaker G, DeRosear L, Mukerji V, Lamberti JW. Major depression in cardiology chest pain patients without coronary artery disease and with panic disorder. J Affective Disord 1987; 13(1): 51-59.
7. Katon W, Hall ML, Russo J, et al. Chest pain: relationship of psychiatric illness to coronary arteriographic results. Am J Med 1988; 84(1): 1-9.
8. Cormier LE, Katon W, Russo J, Hollifield M, Hall ML, Vitaliano PP. Chest pain with negative cardiac diagnostic studies. Relationship to psychiatric illness. J Nerv Ment Dis 1988; 176(6): 351-358.

9. Bass C, Chambers JB, Kiff P, Cooper D, Gardner WN. Panic anxiety and hyperventilation in patients with chest pain: a controlled study. Q J Med 1988; 69(260): 949-959.
10. Lantinga LJ, Sprafkin RP, McCroskery JH, Baker MT, Warner RA, Hill NE. One-year psychosocial follow-up of patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1988; 62(4): 209-213.
11. Herrmann C, Scholz KH, Kreuzer H. [Psychologic screening of patients of a cardiologic acute care clinic with the German version of the Hospital Anxiety and Depression Scale] Psychologisches Screening von Patienten einer kardiologischen Akutklinik mt einer deutchen Fassung der "Hospital Anxiety and Depression" (HAD)-Skala. Psychother Psychosom Med Psychol. 1991; 41(2): 83-92.
12. Alexander PJ, Prabhu SG, Krishnamoorthy ES, Halkatti PC. Mental disorders in patients with noncardiac chest pain. Acta Psychiatr Scan 1994; 89(5): 291-293.
13. Mayou R, Bryant B, Forfar C, Clark D. Non-cardiac chest pain and benign palpitations in the cardiac clinic. Br Heart J 1994; 72: 548-553.
14. Proudfit WL, Bruschke AVG, Sones FM Jr. Clinical course of patients with normal or slightly or moderately abnormal coronary arteriograms: 10-year follow-up of 521 patients. Circulation 1980; 62: 712-717.
15. Pasternak RC, Thibault GE, Savoia M, DeSanctis RW, Hutter AM. Chest pain with angiographically insignificant coronary arterial obstruction. Clinical presentation and long-term follow-up. Am J Med 1980; 68: 813-817.
16. Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary arteriograms: A follow-up study of functional status. N Eng J Med 1980; 303: 1249-1252.
17. Wilcox RG, Roland JM, Hampton JR. Prognosis of patients with "chest pain ?cause". Br Med J 1981; 282: 431-433.
18. Isner JM, Salem DN, Banas JS Jr., Levine HJ. Long-term clinical course of patients with normal coronary arteriography: Follow-up study of 121 patients with normal or nearly normal coronary arteriograms. Am Heart J 1981; 102: 645-653.
19. Bass C, Wade C, Hand D, Jackson G. Patients with angina with normal and near normal coronary arteries: clinical and psychosocial state 12 months after angiography. Br Med J Clin Res Ed. 1983; 287(6404): 1505-1508.
20. Wielgosz AT, Fletcher RH, McCants CB, McKinnis RA, Haney TL, Williams RB. Unimproved chest pain in patients with minimal or no coronary disease: a behavioral phenomenon. Am Heart J 1984; 108(1): 67-72.

21. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. J Am Coll Cardiol 1986; 7(3): 479-483.
22. Van Dorpe A, Piessens J, Willems JL, De Geest H. Unexplained chest pain with normal coronary arteriograms. A follow-up study. Cardiology. 1987; 74(6): 436-443.
23. Faxon DP, McCabe CH, Kreigel DE, Ryan TJ. Therapeutic and economic value of a normal coronary angiogram. Am J Med 1982; 73: 500-505.
24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67(6): 361-370.
25. Goldberg DP. The detection of psychiatric illness by questionnaire. Oxford: Oxford university press, 1972; vol 21).
26. Ormel J, Koeter MW, Van den Brink W, Giel R. Concurrent validity of GHQ-28 and PSE as measures of change. Psychol Med 1989; 19(4): 1007-1013.
27. Ormel J, Koeter MW, Van den Brink W. Measuring change with the General Health Questionnaire (GHQ). The problem of retest effects. Soc Psychiatry Psychiatr Epidemiol 1989; 24(5): 227-232.
28. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. Br J Psychiatr 1976; 128: 280-289.
29. Evers A, Van Vliet-Mulder JC, Ter Laak J. [Documentation of tests and testresearch in the Netherlands] Documentatie van tests en testresearch in Nederland.Assen: Van Gorchum, 1992
30. Van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. J Psychosom Res. 1985; 29(2): 199-206.
31. Schmidt AJ, Lousberg R. [Health-attitude and hypochondrias: Development of the MEGAH-scale] Gezondheidsattitude en hypochondrie. Ontwikkeling van de Maastrichter eigen gezondheidsattitude en hypochondrieschaal. Gedrag en Gezondheid 1993; 21(2): 84-94.
32. Erdman RAM, Duivenvoorden HJ, Verhage F, Kazemier M, Hugenholtz PG. Predictability of beneficial effects in cardiac rehabilitation: a randomised clinical trial of psychological variables. J Cardiopulm Rehabil 1986; 6: 206-213.
33. Wolpe J, Lang PJ. A fear survey schedule for use in behaviour therapy. Behav Res Ther 1964; 2:27-30.
34. Arrindell WA. Dimensional structure and psychopathology correlates of the Fear Survey Schedule (FSS-III) in a phobic population: A factorial definition of agoraphobia. Behav Res Ther 1980; 18(4): 229-242.
35. Arrindell WA, Zwaan EJ. [Phobic factors on the AZU-Fear Questionnaire (AZUV) and Wolpe and Lang's Fear Survey Schedule (FSS-III)] Fobische

dimensies, de AZU-Vreesvragenlijst (AZUV) en Wolpe en Lang's Fear Survey Schedule (FSS-III). Ned Tijdschr Psychol 1982; 37(4): 225-239.
36. Van der Ploeg HM, Defares PB, Spielberger CD. [Manual for the State-Trait Anxiety Inventory (STAI)] Handleiding bij de Zelf-Beoordelings Vragenlijst (ZBV).Lisse: Swets & Zeitlinger, 1986
37. Wald FDM, Mellenbergh GJ. [The shortened version of the Dutch translation of the Profile of Mood States] De verkorte versie van de Nederlandse vertaling van de Profile of Mood States. Ned Tijdschr Psychol 1990; 45: 86-90.
38. Appels A, Hoppener P, Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. 1987; 17(1):15-24.
39. Little RJA. Missing-data adjustments in large surveys. J Bus Econ Stat 1988; 6(3): 287-296.
40. Gardner MJ, Altman DG. Statistics with Confidence: confidence intervals and statistical guidelines.London: British Medical Journal, 1989
41. Cohen J. Statistical power analysis for the behavioral sciences.Hillsdale: Erlbaum, 1988
42. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143(1): 29-36.
43. SPSS-Inc. Statistical package for the social sciences.Chicago: 1990
44. Chambers JB, Kiff PJ, Gardner WN, Jackson G, Bass C. Value of measuring end tidal partial pressure of carbon dioxide as an adjunct to treadmill exercise testing. Br Med J (Clin Res Ed) 1988; 296(6632): 1281-1285.
45. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Effect of hyperventilation and mental stress on coronary blood flow in syndrome X. Br Heart J 1993; 69(6): 516-524.
46. Mayou R. Invited review: Atypical chest pain. J Psychosom Res 1989; 33(4): 393-406.
47. Bass C, Gardner WN, Jackson G. Abnormal breathing patterns associated with angina-like chest pain. Br J Clin Pract. 1986; 40(1): 25-27.
48. Beck JG, Berisford MA, Taegtmeyer H. The effects of voluntary hyperventilation on patients with chest pain without coronary artery disease. Behav Res Ther 1991; 29: 611-621.
49. Moreyra AE, McGough WE, Hosler M, Kostis JB. Clinical improvement of patients with chest pain and normal coronary arteries after coronary arteriography: The possible role of hyperventilation syndrome. Int J Cardiol 1982; 2: 306-308.
50. Bass C, Chambers JB, Gardner WN. Hyperventilation provocation in patients with chest pain and a negative treadmill exercise test. J Psychosom Res 1991; 35(1): 83-89.

51. Fensterheim H, Wiegand B. Group treatment of the hyperventilation syndrome. Int J Group Psychoth 1991; 41(3): 399-403.
52. Girotti LA, Crosatto JR, Messuti H, et al. The hyperventilation test as a method for developing successful therapy in Prinzmetal's angina. Am J Cardiol 1982; 49(4): 834-841.
53. Garssen B, Rijken H. Clinical aspects and treatment of the Hyperventilation Syndrome. Beh Psychoth 1986; 14(1): 46-68.
54. Hegel MT, Abel GG, Etscheidt M, Cohen-Cole S, Wilmer CI. Behavioral treatment of angina-like chest pain in patients with hyperventilation syndrome. J Behav Ther Exp Psychiatry 1989; 20(1): 31-39.

# 4. Empirical psychological modelling of chest pain; a cross-sectional study

*A.W. Serlie, H.J. Duivenvoorden, J. Passchier, F.J. ten Cate, J.W. Deckers, R.A.M. Erdman*

*(submitted)*

## 4.1 Abstract

The psychological profiles of 55 non-cardiac patients (NCA) and 43 patients with coronary artery disease (CAD) were analyzed, in order to construct an empirical-psychological model which would be able to discriminate these two groups at their first visit to the cardiologist. All patients were suffering from chest pain at the time of referral. The NCA patients were significantly younger than the CAD patients and suffered less from chest pain typical for angina pectoris. Additionally, the NCA patients showed significantly higher levels of interpersonal sensitivity, displeasure, fears related to bodily injury, death and illness, depression, fatigue and mood disturbance, but a lower level of vigour than cardiac patients.

Logistic regression on the variables jointly showed that, when adjusted for age and gender, the NCA patients had less chest pain, typical for angina pectoris, less fear of their own health and were less disabled, but had more fears related to bodily injury, death and illness and more fatigue. With this model approximately 80% of the patients could be correctly classified as having cardiac or non-cardiac causes for their chest pain complaints; an improvement of 54% compared to the prior probability. Crossvalidation showed that the constructed model was stable.

## 4.2 Introduction

Chest pain without a clear somatic cause has come a long way since it was first named "muscular exhaustion of the heart" back in the eighteen sixties by

Hartstone (1) and Stillé (2) in their pioneering research of the disorder among soldiers. Since then the disorder has been diversely labelled, corresponding with the reasons thought to be underlying the disorder (3). Lewis (4) for instance called the disorder "effort syndrome" as he believed that all the syndrome's clinical features were those normally produced by effort, but in the affected soldiers occurred on very slight effort. There are several synonyms such as irritable heart (5), Da Costa's syndrome, soldier's heart and neurocirculatory asthenia (6).

The recent literature, however, prefers to define the disorder in terms of psychogenicity; cardiac neurosis, cardiophobia or just simply non-cardiac chest pain (7-13). These studies have shown that the prevalence of normal or minimally diseased coronary arteries in patients with chest pain is 30 percent. Non-cardiac chest pain patients are relatively young, more often female, often suffer relatively frequently from panic disorder, hyperventilate, are considered to be depressed and anxious and have a higher prevalence of atypical chest pain (7-11, 14-21).

Although the prospects of survival for these patients are favourable (15, 17, 22-30), patients' symptoms do tend to persist or even increase in severity over the years. Apart from the risk of somatic fixation (31), the often unnecessary medical consumption lays a financial burden on society (32).

Most of the studies mentioned above only signal the differences between the cardiac and non-cardiac chest pain patients, but do not quantitatively relate them to a model comprising variables with differential potential. In a previous study (21) the psychological profiles of patients were assessed on average 1.3 years after their first consultation by the cardiologist. Patients were familiar with the fact whether their complaints were of a somatic nature or not. In that study we were able to exploratively construct a model that correctly classified 75% of the chest pain patients as being either cardiac or non-cardiac. The performance was established by age, gender, hyperventilation and anxiety.

In the present study our aim was to construct a similar quantitative model which could be used at the first consultation by the cardiologist in order to help discriminate patients with non-cardiac chest pain complaints from patients with chest pain of a somatic nature. For that reason we assessed the patients' demographic and psychological characteristics at the first consultation at the cardiology out-patients' clinic, without the patient having any knowledge of the outcome of the diagnostic tests.

## 4.3 Methods

### 4.3.1 Patients

Eligible for this study were patients who had been referred to the cardiology out-patients' clinic of the Rotterdam University Hospital 'Dijkzigt', for the first time, from November 1992 up to February 1995, with chest pain as a chief complaint. Inclusion criteria were; sufficient proficiency of the Dutch language, age over 18 or under 75 years, no prior history of coronary artery disease or other organic heart diseases, other somatic causes, such as lung or oesophagus problems, for their chest pain complaints or a history of psychiatric illness.

In total 504 patients were referred to the out-patients' clinic during the study period. Of those, 193 patients were referred for chest pain. Cardiologic testing showed that 47 patients had another somatic, non-cardiac cause for their complaints, One hundred and forty six patients met the study's inclusion criteria and were therefore eligible for this study. All diagnoses were derived from the medical records and checked against the diagnosis code of the Thoraxcentre medical database. As a consequence, eighty eight patients were classified non-cardiac (NCA) and 58 as having coronary artery disease (CAD). After elimination of patients unwilling to participate ($n_{nca}=22$; $n_{cad}=8$) and inconclusive data ($n_{nca}=11$; $n_{cad}=7$), the data of 55 non-cardiac patients (27 men, 28 women; mean age 49.9 yrs, SD 11.8) and 43 cardiac patients (25 men, 18 women; mean age 63.5 yrs, SD 8.0) were used for statistical analysis.

### 4.3.2 Procedure

At the first visit to the cardiology out-patients' clinic the patient was informed about the study by the first author (A.S.) and presented questionnaires gathered in a booklet. The patients were requested to fill out the questionnaires, to the best of their ability, and return them in an enclosed pre-paid envelope within one week.

### 4.3.3 Cardiological assessment

All patients underwent standard electrocardiogram testing. Seventy eight of the 98 (80%) patients underwent an exercise test, 9 (9%) angiography and 11 (11%) other cardiac testing such as dobutamine stress testing, to determine the nature of their complaints. The cardiologist's final diagnosis was assessed from

the patient's medical record and used to classify the patients as either having 1) complaints induced by somatic causes, other than cardiac e.g. lung or oesophagus problems, 2) cardiac or 3) non-cardiac causes. For answering the objectives of this study only the last two categories were of interest.

Chest pain typical for angina was assessed by means of the Rose questionnaire (33). In this questionnaire patients are asked questions concerning their type of chest pain. Typical chest pain is defined present when patients indicate having chest pain a) when walking or hurrying, b) reduction of the pain within 10 minutes when resting and c) located at the sternum or left anterior chest and left arm.

### 4.3.4 Psychological assessment

On the basis of earlier findings, concerning the aetiology of non-cardiac chest pain (7-11, 14-18, 21), psychological characteristics were measured with the following questionnaires, being operationalisations the constructs of relevance (see appendix for details).

The Hospital Anxiety Depression Scale (HAD) (34), was used to assess anxiety and depression. Psychopathology was measured with the General Health Questionnaire (GHQ-12). The Symptom Checklist (SCL-90) (35) was used to assess agoraphobia, anxiety, depression, somatisation, obsessive compulsive behaviour, interpersonal sensitivity, hostility, sleeping-problems and psychoneuroticism. Hyperventilation was measured with the Nijmegen Questionnaire (NQ) (36). Hypochondria was assessed with the Maastricht hypochondria scale (MEGAH) (37). Five scales assess; 'fear of own health', 'general health fear', 'illness belief', 'confidence in doctors' and 'search of medical information'. The sum of the first three subscales is a measure for the amount of hypochondria. Displeasure and feelings of physical disability were assessed with subscales of the Heart Patients Psychological Questionnaire (HPPQ) (38). Two subscales of the Fear Survey Schedule (FSS) (39-41) were used to assess 'fear related to bodily injury, death and illness' and 'social anxiety'. By means of the Profile Of Mood States (POMS) (42) depression, anger, fatigue, vigour and tension were measured.

### 4.3.5 Statistical analysis

Before answering the research questions, missing data were estimated for variables of which the percentage missing was below 15%. If the percentage

missing was larger than 15% the variable was removed from analysis. For estimating the values of the missing data the predicted mean matching method was used (43). Other variables were utilised as predictors for the missing variables. Regression analysis, with the procedure backwards elimination, was used for this purpose. Only predictor variables that were significant at 0.05 level were maintained in the regression model.

For both the NCA and the CAD group the means including the 95% confidence intervals and the confidence intervals for the difference are presented. The statistical significance is defined as whether the 95% confidence interval of the difference includes the value 0.0 or not (44). In addition the magnitude of the difference between the two groups of patients is calculated using Cohen's $\delta$ (45). The differences between the two groups were also assessed by means of a oneway analysis of variance (46).

Furthermore, all psychological variables and typical chest pain were examined by means of a logistic regression analysis. With this multivariate modelling technique an estimation of the probability of an event (cardiac or non-cardiac) occurring can be made. Standard scores of the variables were used in the analyses, in order to be able to more easily compare estimated coefficients ($\beta$). In the analyses the backward elimination procedure was used. Here too, only predictor variables that were significant at 0.05 level were maintained in the model.

The variables significantly contributing to the model were subsequently analyzed again by means of a logistic regression analysis to be able to adjust the model for age and gender. This was done by calculating the predicted probability using the new regression coefficients for the psychological variables, while setting them to zero for age and gender.

Thereafter, a receiver-operator characteristic (ROC) curve was constructed for psychological characteristics adjusted for age and gender. The logistic model calculated the predicted probability of being a non-cardiac patient for all subjects and subsequently sensitivity and specificity were calculated. In the ROC curve, the true-positive rate (sensitivity) is plotted against the false-positive rate (1 minus specificity) and the discriminative ability of a test is shown by the position of the full curve: the farther upward and to the left the curve lies in the figure, the more optimal the test. Thus, the area under the ROC-curve reflects the performance of the model, in a sense that a larger surface area reflects a higher performance (47).

Finally, the model was crossvalidated by randomly assigning patients into five strata, comprising the same proportion of non-cardiac/cardiac and male/female patients as the total group. A model was constructed based on four of these strata and the probabilities of the fifth stratum were then estimated based on the constructed model. This procedure was followed for all five possible combinations. Subsequently, the estimated probabilities were tested against the probabilities of the model based on all patients, using a regression analysis

All data were analyzed using the SPSS/PC programme (46).

**Table 4.1** *Demographic characteristics of non-cardiac and cardiac patients*

| | NCA (n=55) | CAD (n=43) | P |
|---|---|---|---|
| Age (mean(±SD)) | 49.89 (11.8) | 63.47 (8.0) | $\ll 0.01$ |
| Gender (male:female) | 27:28 | 25:18 | 0.49 |
| Marital status (partner:single) | 45:10 | 35:8 | 1.00 |
| Full time employment (yes:no) | 24:31 | 6:37 | $< 0.01$ [a] |
| Smoking (yes:ex:non) | 12:24:19 | 7:24:12 | 0.48 |
| Typical chest pain (yes:no) | 8:47 | 20:23 | $< 0.01$ [b] |

[a] $\chi^2 = 8.66$ df = 1
[b] $\chi^2 = 12.16$ df = 1

## 4.4 Results

Table 4.1 shows the general characteristics of the two categories of patients. Consistent with findings in earlier studies (7-11, 14-18), the non-cardiac patients were significantly younger ($F(1,96)=41.88$; $p \ll 0.01$) and their chest pain was less typical for angina pectoris ($\chi^2 = 12.16$; $p < 0.01$). Significantly more non-cardiac patients (44%) were engaged in full-time employment compared to the cardiac patients (14%). This was, however, due to a larger proportion of retired cardiac patients ($\chi^2=4.21$; $p<0.05$). Furthermore, the two groups were comparable in gender ratio, marital status and smoking behaviour.

In Table 4.2 the psychological characteristics for both groups can be found. As can be seen non-cardiac patients show significantly higher levels of interpersonal sensitivity ($F(1,96)=3.95$; $p<0.05$), displeasure ($F(1,96)=7.41$;

**Table 4.2** *Psychological characteristics of NCA and CAD patients*

| Determinant | Non-cardiac | | Cardiac | | | | |
|---|---|---|---|---|---|---|---|
| | $\bar{x}_{nca}$ | 95% CI | $\bar{x}_{cad}$ | 95% CI | Cohen δ | 95% CI | P |
| **HAD** | | | | | | | |
| Anxiety | 7.82 | 6.68; 8.96 | 6.51 | 5.35; 7.67 | 0.33 | -0.32; 2.94 | 0.11 |
| Depression | 5.35 | 4.35; 6.35 | 5.23 | 4.31; 6.15 | 0.03 | -1.28; 1.52 | 0.87 |
| **GHQ** | | | | | | | |
| Psychopathology | 4.02 | 2.94; 5.10 | 3.19 | 2.15; 4.23 | 0.22 | -0.69; 2.35 | 0.28 |
| **SCL-90** | | | | | | | |
| Agoraphobia | 9.39 | 8.17; 10.61 | 8.29 | 7.67; 8.91 | 0.30 | -0.39; 2.59 | 0.14 |
| Anxiety | 17.26 | 15.26; 19.26 | 15.20 | 13.68; 16.72 | 0.32 | -0.58; 4.70 | 0.12 |
| Depression | 26.85 | 23.95; 29.75 | 23.42 | 21.42; 25.42 | 0.37 | -0.30; 7.16 | 0.07 |
| Somatisation | 24.03 | 21.69; 26.37 | 22.49 | 20.13; 24.85 | 0.19 | -1.83; 4.91 | 0.37 |
| Obses. compuls. | 15.67 | 13.83; 17.51 | 13.98 | 12.62; 15.34 | 0.29 | -0.72; 4.10 | 0.16 |
| Interp. sensitiv. | 25.58 | 23.08; 28.08 | 22.50 | 21.14; 23.86 | 0.41 | 0.00; 6.16 | <0.05 |
| Hostility | 8.11 | 7.35; 8.87 | 7.42 | 6.84; 8.00 | 0.28 | -0.32; 1.70 | 0.17 |
| Sleepproblems | 6.63 | 5.77; 7.49 | 5.85 | 4.93; 6.77 | 0.25 | -0.49; 2.05 | 0.22 |
| Psychoneurot | 146.18 | 132.70;159.60 | 131.66 | 123.00;140.30 | 0.35 | -2.41; 31.45 | 0.09 |
| **NQ** | | | | | | | |
| Hypervent. | 22.23 | 19.23; 25.23 | 18.91 | 15.65; 22.17 | 0.30 | -1.15; 7.79 | 0.14 |
| **MEGAH** | | | | | | | |
| Fear own health | 47.66 | 44.80; 50.52 | 48.63 | 45.61; 51.65 | -0.09 | -5.16; 3.22 | 0.64 |
| Med. informat. | 11.95 | 11.19; 12.71 | 10.67 | 9.25; 12.09 | 0.34 | -0.24; 2.80 | 0.10 |
| Confid. in doctors | 21.57 | 20.29; 22.85 | 22.20 | 20.52; 23.88 | -0.12 | -2.69; 1.43 | 0.55 |
| Illness belief | 25.47 | 23.77; 27.17 | 24.83 | 22.93; 26.73 | 0.10 | -1.92; 3.20 | 0.62 |
| Gen. health | 41.45 | 37.95; 44.95 | 37.07 | 33.67; 40.47 | 0.36 | -0.59; 9.35 | 0.08 |
| Hypoch index | 114.21 | 107.60;120.80 | 110.62 | 103.40;117.80 | 0.15 | -6.19; 13.37 | 0.46 |
| **HPPQ** | | | | | | | |
| Disability | 25.56 | 23.76; 27.36 | 27.48 | 25.72; 29.24 | -0.30 | -4.49; 0.65 | 0.14 |
| Displeasure | 16.41 | 15.23; 17.59 | 14.20 | 13.14; 15.26 | 0.55 | 0.58; 3.84 | <0.01 |
| **FSS** | | | | | | | |
| Fear bod injury | 22.41 | 20.29; 24.53 | 18.33 | 16.85; 19.81 | 0.61 | 1.35; 6.81 | <0.01 |
| Social anxiety | 22.00 | 19.66; 24.34 | 19.58 | 17.96; 21.20 | 0.33 | -0.58; 5.42 | 0.11 |
| **POMS** | | | | | | | |
| Depression | 5.29 | 3.59; 6.99 | 2.92 | 1.54; 4.30 | 0.42 | 0.08; 4.66 | <0.05 |
| Anger | 4.12 | 2.78; 5.46 | 3.81 | 2.25; 5.37 | 0.06 | -1.74; 2.36 | 0.77 |
| Fatigue | 8.27 | 6.53; 10.01 | 5.49 | 3.69; 7.29 | 0.45 | 0.25; 5.31 | <0.05 |
| Vigour | 8.71 | 7.51; 9.91 | 11.09 | 9.71; 12.47 | -0.53 | -4.21; -0.55 | <0.05 |
| Tension | 6.76 | 5.42; 8.10 | 5.04 | 3.76; 6.32 | 0.37 | -0.17; 3.61 | 0.07 |
| Total mood dist | 35.74 | 29.70; 41.78 | 26.17 | 20.75; 31.59 | 0.47 | 1.22; 17.92 | <0.05 |

$p<0.01$), fears related to bodily injury, death and illness ($F(1,96)=8.97$; $p<0.01$), depression measured with the POMS ($F(1,96)=4.29$; $p<0.01$), fatigue ($F(1,96)=4.84$; $p<0.05$), and total mood disturbance ($F(1,96)=5.25$; $p<0.05$), but a significantly lower level of vigour ($F(1,96)=6.81$; $p<0.05$).

**Table 4.3** *Differential qualities for psychological determinants unadjusted and adjusted for age and gender.*

| Determinant | $\beta$ | | exp $\beta$ | | SE | | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| | unadj | adj | unadj | adj | unadj | adj | unadjusted | adjusted |
| Typical Angina | -1.42 | -1.02 | 0.24 | 0.36 | 0.39 | 0.39 | 0.11 ; 0.53* | 0.17 ; 0.79* |
| HAD Anxiety | 1.03 | 0.72 | 2.80 | 2.05 | 0.40 | 0.42 | 1.26 ; 6.23* | 0.89 ; 4.76 |
| Fear own health | 1.07 | 0.98 | 2.92 | 2.66 | 0.44 | 0.47 | 1.21 ; 7.03* | 1.04 ; 6.82* |
| Disability | -1.59 | -1.21 | 0.20 | 0.30 | 0.46 | 0.47 | 0.08 ; 0.51* | 0.12 ; 0.76* |
| Fear of bodily Injury | 1.40 | 1.27 | 4.06 | 3.56 | 0.46 | 0.45 | 1.62 ; 10.18* | 1.45 ; 8.76* |
| Fatigue | 1.12 | 1.05 | 3.06 | 2.86 | 0.45 | 0.50 | 1.25 ; 7.54* | 1.05 ; 7.77* |
| Vigour | -1.01 | -0.63 | 0.36 | 0.53 | 0.40 | 0.39 | 0.16 ; 0.81* | 0.24 ; 1.16 |

* significant at 0.05 level

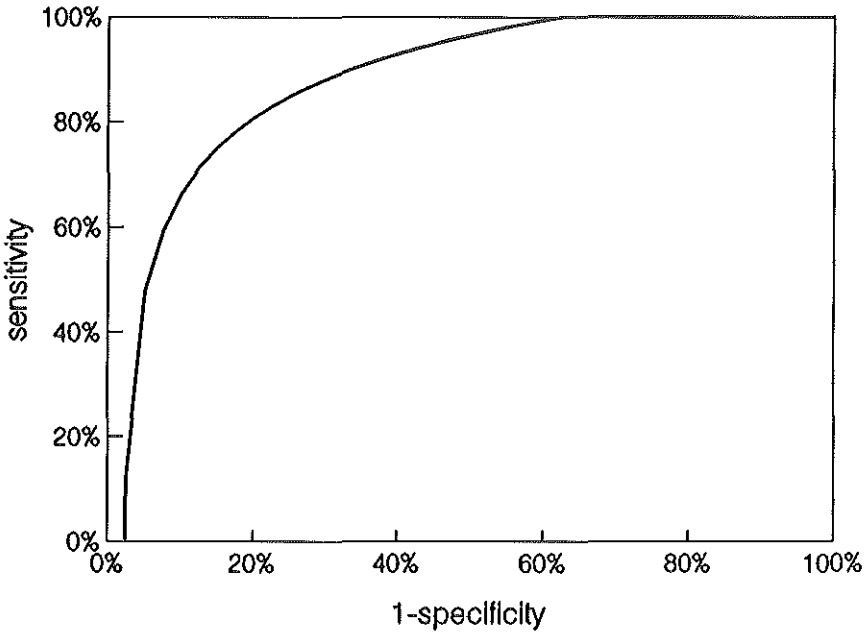
There was a trend for non-cardiac patients to have a higher score for depression on the SCL-90 ($F(1,96)=3.36$; $p=0.07$), psychoneuroticism ($F(1,96)=2.93$; $p=0.09$), and tension ($F(1,96)=3.36$; $p=0.07$) and to have less general health fear ($F(1,96)=3.10$; $p=0.08$) as indicated by a higher score on the MEGAH subscale.

Using the backward elimination, logistic regression method of analysis with the criterion variable cardiac (yes/no) and all psychological variables and typical chest pain as the predictor variables, typical chest pain ($\beta=-1.42$), HAD-anxiety ($\beta=1.03$), fear of own health ($\beta=1.07$), feelings of physical disability ($\beta=-1.59$), fears related to bodily injury, death and illness ($\beta=1.40$), fatigue ($\beta=1.12$) and vigour ($\beta=-1.01$) remained in the model, giving an overall correct classification of 83.5%. Taking the prior probability of 56.1% into account the model shows an improvement of 62% ((83.5-56.1) / (100-56.1) $\times$100%) compared to the prior probability.

When adjusted for age and gender, only typical chest pain, fear of own health, feelings of physical disability, fear of bodily injury, death and illness' and fatigue contributed significantly to the predictability of non-cardiac chest pain (see Table 4.3). The overall correct classification was 79.6%.

In Figure 4.1 the ROC-curve for the adjusted model is shown. The area under the adjusted ROC-curve is 0.90 (95% CI: 0.84 to 0.96), indicating a

**Figure 4.1** *Receiver Operator Characteristic Curve of the model adjusted for age and gender*



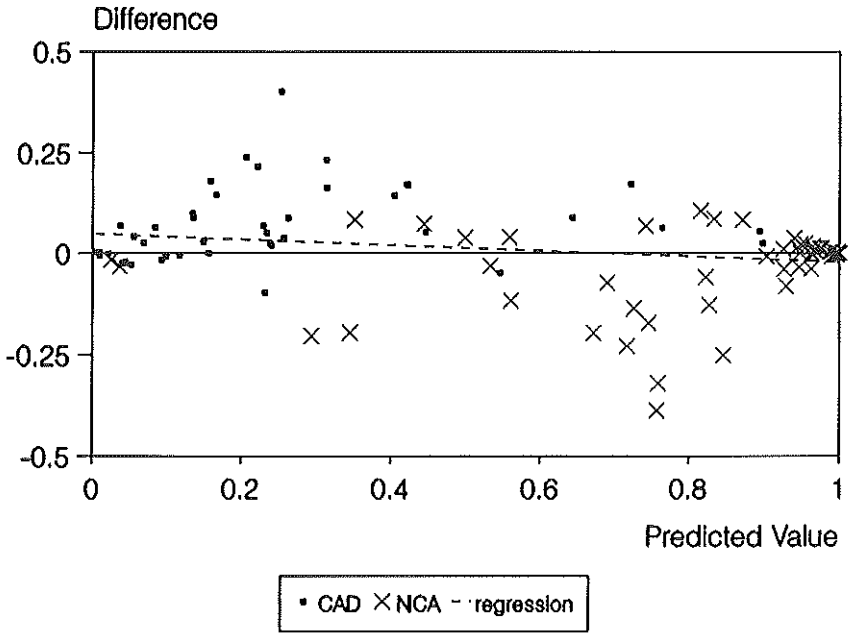

high performance.

Figure 4.2 shows the difference between the predicted probability acquired by crossvalidation and the predicted probability derived form the final logistic model. The small $\beta$ (-0.07; 95% CI -0.13 to -0.01) and intercept (0.05; 95% CI 0.01 to 0.09) of the regression line is an indication that the constructed model is stable, although there is a slight negative association in the sense that the probability being non-cardiac is slightly underestimated and the probability of being cardiac is estimated a little too high.

## 4.5 Discussion

In this study we have tried to quantitatively construct an empirical-psychological model which can, at first consultation by a cardiologist, predict to a high degree whether a patient's chest pain complaints are of a cardiac or a non-cardiac nature. Logistic regression analyses showed that, adjusted for age

**Figure 4.2** *Predicted probability of being a NCA patient set against the difference between the predicted value of the final model and the crossvalidated model for both the CAD (■) and the NCA (×) patients.*




and gender, chest pain typical for angina pectoris, fear of one's own health, feelings of physical disability, fears related to bodily injury, death and illness and fatigue are the foremost psychological variables that differentiate between the two groups with an overall correct classification of almost 80%. A smaller proportion of non-cardiac patients has chest pain complaints typical for angina pectoris. Additionally, they are less preoccupied with their own health, as derived from information about hypochondria, and show less feelings of physical disability. On the other hand the non-cardiac patients have more fears related to bodily injury, death and illness and show more fatigue.

The results of the present study are not completely compatible with most earlier studies (16, 21, 48-54) in which non-cardiac patients were found to suffer significantly more from hyperventilation, somatisation and general anxiety disorders than cardiac patients. In line with our study, however, the results of a study by Tennant et al. (55), of 532 patients with ischaemia-like

chest pain, showed that no significant differences could be found between cardiac and non-cardiac patients on measures for anxiety and neuroticism.

In the present study, the non-cardiac patients were found to be more depressed than the cardiac patients. This is in line with previous studies (8, 10, 11, 16, 17, 19). The higher fatigue and displeasure of the non-cardiac patients may also be a manifestation of depression, as they are part of the criteria for major depression as defined by DSM-III-R (56).

In our view the main difference between the present study and previous studies is the time of filling out the questionnaires, in relation the knowledge of the diagnosis. In the present study all patients were asked to fill out the questionnaires immediately after their first consultation by the cardiologist. It can therefore be assumed that the patients have practically no knowledge of whether their complaints were of a somatic nature or not. All further diagnostic testing took place at a later stage. Additionally, the method of diagnostic testing did not significantly differ for both patient categories. When reviewing previous studies on the difference between cardiac and non-cardiac patients, the psychological testing appears to have been conducted quite late in the stage of diagnostic testing. In Bass' study (7) for instance, psychological testing was conducted 24 hours following arteriography. The same was true for Lantinga's study (17). In Katon's study (10) in which the psychological testing was also conducted after arteriography, the researchers were blind with regard to the patient's diagnosis, whereas, the patients themselves had been informed about the preliminary results of the arteriography.

A possible indication for the impact of the diagnosis may be found when comparing the results of an earlier study of non-cardiac and cardiac patients, conducted by our research group (21), in which the same questionnaires were used as in the present study. In the earlier study the patients were seen on average 1.3 years after their first consultation by the cardiologist and at the time of psychological assessment knew what their diagnosis was. The non-cardiac patients showed significantly higher levels of anxiety, somatisation, psychoneuroticism and hyperventilation, consistent with earlier studies (16, 48-54). When comparing the present study with our earlier study, the knowledge of the diagnosis presumably generates a shift in the non-cardiac group from more general psychological problems (fears related to bodily injury, death and illness, fatigue and depression) to a more somatoform expression of these problems (somatisation, hyperventilation). For the cardiac group once the

diagnosis is known and treated, there seems to be a lower level of hyperventilation, somatisation and feelings of physical disability. This is possibly due to the legitimacy of the chest pain complaints and the pain reduction procured by adequate medical treatment, both lacking for the non-cardiac patient.

With the model constructed in this study we have tried to present a means by which non-cardiac patients can be discriminated from cardiac patients in the early stages of establishing the final diagnosis. Early detection of non-cardiac patients and recognition of the underlying psychological issues is important as appropriate psychological or psychiatric treatment (see e.g. (57-60)) has shown to be effective and may in turn lead to a reduction of unnecessary medical consumption.

## 4.6 References

1. Hartstone H. On heart disease in the army. Am J Med Sci 1864; 48:89-92.
2. Stillé A. Address before the Philadelphia Country Medical Society. In. Philadelphia: Collins, Printer, 1863:18-19.
3. Serlie AW, Erdman RAM, Passchier J, Trijsburg RW, Ten Cate FJ. Psychological aspects of non-cardiac chest pain. Psychother Psychosom 1995; 64:62-73.
4. Lewis T. The soldier's heart and the effort syndrome. New York: Paul B. Hoeber, 1919: 1-103.
5. Da Costa JM. On irritable heart: a clinical study of a form of functional cardiac disorder and its consequences. Am J Med Sci 1871; 61(121):17-52.
6. Levine SA. The origin of the term neurocirculatory asthenia. N Eng J Med 1965; 273:604-605.
7. Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med. 1984; 14(1):51-61.
8. Channer KS, Papouchado M, James MA, Rees JR. Anxiety and depression in patients with chest pain referred for exercise testing. Lancet 1985; 2(8459):820-823.
9. Beitman BD, Basha I, Flaker G, DeRosear L, Mukerji V, Lamberti JW. Major depression in cardiology chest pain patients without coronary artery disease and with panic disorder. J Affective Disord 1987; 13(1):51-59.

10. Katon W, Hall ML, Russo J, et al. Chest pain: relationship of psychiatric illness to coronary arteriographic results. Am J Med 1988; 84(1):1-9.
11. Cormier LE, Katon W, Russo J, Hollifield M, Hall ML, Vitaliano PP. Chest pain with negative cardiac diagnostic studies. Relationship to psychiatric illness. J Nerv Ment Dis 1988; 176(6):351-358.
12. Eifert GH. Cardiophobia: An anxiety disorder in its own right? Special Issue: Research in anxiety and fear. Behav Change 1991; 8(3):100-116.
13. Potts SG, Bass CM. Psychological morbidity in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. Psych Med 1995; 25(2):339-347.
14. Costa PT, Zonderman AB, Engel BT, Baile WF, Brimlow DL, Brinker J. The relation of chest pain symptoms to angiographic findings of coronary artery stenosis and neuroticism. Psychosom Med. 1985; 47(3):285-293.
15. Papanicolaou MN, Califf RM, Hlatky MA, et al. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. Am J Cardiol 1986; 58(13):1181-1187.
16. Bass C, Chambers JB, Kiff P, Cooper D, Gardner WN. Panic anxiety and hyperventilation in patients with chest pain: a controlled study. Q J Med 1988; 69(260):949-959.
17. Lantinga LJ, Sprafkin RP, McCroskery JH, Baker MT, Warner RA, Hill NE. One-year psychosocial follow-up of patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1988; 62(4): 209-213.
18. Herrmann C, Scholz KH, Kreuzer H. [Psychologic screening of patients of a cardiologic acute care clinic with the German version of the Hospital Anxiety and Depression Scale] Psychologisches Screening von Patienten einer kardiologischen Akutklinik mt einer deutchen Fassung der "Hospital Anxiety and Depression" (HAD)-Skala. Psychother Psychosom Med Psychol. 1991; 41(2): 83-92.
19. Alexander PJ, Prabhu SG, Krishnamoorthy ES, Halkatti PC. Mental disorders in patients with noncardiac chest pain. Acta Psychiatr Scan 1994; 89 (5):291-293.
20. Mayou R, Bryant B, Forfar C, Clark D. Non-cardiac chest pain and benign palpitations in the cardiac clinic. Br Heart J 1994; 72:548-553.
21. Serlie AW, Duivenvoorden HJ, Passchier J, Ten Cate FJ, Deckers JW, Erdman RAM. Empirical psychological modelling of chest pain; a comparative study. J Psychosom Res (in press).
22. Proudfit WL, Bruschke AVG, Sones FM Jr. Clinical course of patients with normal or slightly or moderately abnormal coronary arteriograms: 10-year follow-up of 521 patients. Circulation 1980; 62:712-717.

23. Pasternak RC, Thibault GE, Savoia M, DeSanctis RW, Hutter AM. Chest pain with angiographically insignificant coronary arterial obstruction. Clinical presentation and long-term follow-up. Am J Med 1980; 68:813-817.
24. Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary arteriograms: A follow-up study of functional status. N Eng J Med 1980; 303:1249-1252.
25. Wilcox RG, Roland JM, Hampton JR. Prognosis of patients with "chest pain ?cause". Br Med J 1981; 282:431-433.
26. Isner JM, Salem DN, Banas JS Jr., Levine HJ. Long-term clinical course of patients with normal coronary arteriography: Follow-up study of 121 patients with normal or nearly normal coronary arteriograms. Am Heart J 1981; 102: 645-653.
27. Bass C, Wade C, Hand D, Jackson G. Patients with angina with normal and near normal coronary arteries: clinical and psychosocial state 12 months after angiography. Br Med J Clin Res Ed. 1983; 287(6404):1505-1508.
28. Wielgosz AT, Fletcher RH, McCants CB, McKinnis RA, Haney TL, Williams RB. Unimproved chest pain in patients with minimal or no coronary disease: a behavioral phenomenon. Am Heart J 1984; 108(1):67-72.
29. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. J Am Coll Cardiol 1986; 7(3):479-483.
30. Van Dorpe A, Piessens J, Willems JL, De Geest H. Unexplained chest pain with normal coronary arteriograms. A follow-up study. Cardiology. 1987; 74(6):436-443.
31. Eifert GH. Cardiophobia: a paradigmatic behavioural model of heart-focused anxiety and non-anginal chest pain. Behav Res Ther 1992; 30(4):329-345.
32. Faxon DP, McCabe CH, Kreigel DE, Ryan TJ. Therapeutic and economic value of a normal coronary angiogram. Am J Med 1982; 73:500-505.
33. Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. Geneva: World health organization, 1982. .
34. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67(6):361-370.
35. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. Br J Psychiatr 1976; 128:280-289.
36. Van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. J Psychosom Res. 1985; 29(2): 199-206.
37. Schmidt AJ, Lousberg R. [Health-attitude and hypochondrias: Development of the MEGAH-scale] Gezondheidsattitude en hypochondrie. Ontwik-

keling van de Maastrichter eigen gezondheidsattitude en hypochondrie--schaal. Gedrag en Gezondheid 1993; 21(2):84-94.
38. Erdman RAM, Duivenvoorden HJ, Verhage F, Kazemier M, Hugenholtz PG. Predictability of beneficial effects in cardiac rehabilitation: a randomised clinical trial of psychological variables. J Cardiopulm Rehabil 1986; 6: 206-213.
39. Wolpe J, Lang PJ. A fear survey schedule for use in behaviour therapy. Behav Res Ther 1964; 2:27-30.
40. Arrindell WA. Dimensional structure and psychopathology correlates of the Fear Survey Schedule (FSS-III) in a phobic population: A factorial definition of agoraphobia. Behav Res Ther 1980; 18(4):229-242.
41. Arrindell WA, Zwaan EJ. [Phobic factors on the AZU-Fear Questionnaire (AZUV) and Wolpe and Lang's Fear Survey Schedule (FSS-III)] Fobische dimensies, de AZU-Vreesvragenlijst (AZUV) en Wolpe en Lang's Fear Survey Schedule (FSS-III). Ned Tijdschr Psychol 1982; 37(4):225-239.
42. Wald FDM, Mellenbergh GJ. [The shortened version of the Dutch translation of the Profile of Mood States] De verkorte versie van de Nederlandse vertaling van de Profile of Mood States. Ned Tijdschr Psychol 1990; 45:86-90.
43. Little RJA. Missing-data adjustments in large surveys. J Bus Econ Stat 1988; 6(3):287-296.
44. Gardner MJ, Altman DG. Statistics with Confidence: confidence intervals and statistical guidelines. London: British Medical Journal, 1989. .
45. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale: Erlbaum, 1988.
46. SPSS-Inc. Statistical package for the social sciences. Chicago, 1990. .
47. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143(1):29-36.
48. Chambers JB, Kiff PJ, Gardner WN, Jackson G, Bass C. Value of measuring end tidal partial pressure of carbon dioxide as an adjunct to treadmill exercise testing. Br Med J (Clin Res Ed) 1988; 296(6632):1281-1285.
49. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Effect of hyperventilation and mental stress on coronary blood flow in syndrome X. Br Heart J 1993; 69(6):516-524.
50. Mayou R. Invited review: Atypical chest pain. J Psychosom Res 1989; 33(4): 393-406.
51. Bass C, Gardner WN, Jackson G. Abnormal breathing patterns associated with angina-like chest pain. Br J Clin Pract. 1986; 40(1):25-27.
52. Beck JG, Berisford MA, Taegtmeyer H. The effects of voluntary hyperventilation on patients with chest pain without coronary artery disease. Behav Res Ther 1991; 29:611-621.

53. Moreyra AE, McGough WE, Hosler M, Kostis JB. Clinical improvement of patients with chest pain and normal coronary arteries after coronary arteriography: The possible role of hyperventilation syndrome. Int J Cardiol 1982; 2:306-308.
54. Bass C, Chambers JB, Gardner WN. Hyperventilation provocation in patients with chest pain and a negative treadmill exercise test. J Psychosom Res 1991; 35(1):83-89.
55. Tennant C, Mihailidou A, Scott A, et al. Psychological symptom profiles in patients with chest pain. J Psychosom Res 1994; 38(4):365-371.
56. APA. Diagnostic and statistical manual of mental disorders, 3rd ed. Revised. Washington DC: APA, 1987. .
57. Fensterheim H, Wiegand B. Group treatment of the hyperventilation syndrome. Int J Group Psychoth 1991; 41(3):399-403.
58. Girotti LA, Crosatto JR, Messuti H, et al. The hyperventilation test as a method for developing successful therapy in Prinzmetal's angina. Am J Cardiol 1982; 49(4):834-841.
59. Garssen B, Rijken H. Clinical aspects and treatment of the Hyperventilation Syndrome. Beh Psychoth 1986; 14(1):46-68.
60. Hegel MT, Abel GG, Etscheidt M, Cohen-Cole S, Wilmer CI. Behavioral treatment of angina-like chest pain in patients with hyperventilation syndrome. J Behav Ther Exp Psychiatry 1989; 20(1):31-39.
61. Goldberg DP. The detection of psychiatric illness by questionnaire. Oxford: Oxford university press, 1972. (vol 21).
62. Ormel J, Koeter MW, Van den Brink W, Giel R. Concurrent validity of GHQ-28 and PSE as measures of change. Psychol Med 1989; 19(4): 1007-1013.
63. Ormel J, Koeter MW, Van den Brink W. Measuring change with the General Health Questionnaire (GHQ). The problem of retest effects. Soc Psychiatry Psychiatr Epidemiol 1989; 24(5):227-232.
64. Evers A, Van Vliet-Mulder JC, Ter Laak J. [Documentation of tests and testreseach in the Netherlands] Documentatie van tests en testresearch in Nederland. Assen: Van Gorchum, 1992.

## 4.7 Appendix

The Hospital Anxiety Depression Scale (HAD) (34), consists of 14 questions, seven reflecting anxiety and seven depression. The answer possibilities indicate the intensity of the given mood; the sum of the individual scores give an overall anxiety (min 0; max 21) and depression (min 0; max 21) score. Validity and reliability have been proven for British and German studies (8, 18).

The General Health Questionnaire (GHQ-12) measures psychopathology. The twelve items of this self-rating questionnaire reflect a measure of severity of functional non-psychotic psychopathology. The questions relate to unusual or unpleasant psychological experiences. Patients are requested to answer by indicating, on a four point

scale, the difference between their present situation compared to their normal situation, choosing from 'none'(coded 0), 'no more than usual'(coded 0), 'more than usual' (coded 1) and 'a lot more than usual' (coded 1) (61). The range of the total scores was 0 to 12. Validity and reliability for the Dutch version have been demonstrated (62, 63).

The Symptom Checklist (SCL-90) (35) assesses agoraphobia (min 7; max 35), anxiety (min 10; max 50), depression (min 16; max 80), somatisation (min 12; max 60), obsessive compulsive behaviour (min 9; max 45), interpersonal sensitivity (min 18; max 90), hostility (min 6; max 30), sleeping-problems (min 3; max 15) and the total of all subscales, including the residual items; psychoneuroticism (min 90; max 450). The SCL-90 is a widely used self-report questionnaire in medical research, to categorize and quantify psychological distress. Patients rate on a five-point Likert scale (1 = not at all, 5 = extremely) the degree of distress they have experienced in the preceding week, from each of 90 items. Validity and reliability have proven to be good for the Dutch population (64).

The Nijmegen Questionnaire (NQ) (36) measures hyperventilation. The questionnaire comprises 16 complaints whose frequency of incidence can be indicated on a 0 to 4 Likert scale (never, rarely, sometimes, often and very frequently). The complaints relate to different systems; (a) cardiovascular e.g. 'palpitations'; (b) neurological, e.g. 'dizzy spells', tingling fingers'; (c) respiratory e.g. 'shortness of breath'; (d) gastro-intestinal, e.g. bloated abdominal sensation'; (e) psyche, e.g. 'tense' and 'anxious feeling'. Total scores can range from 0 to 64. In Van Dixhoorn and Duivenvoorden's study (36) the sensitivity of the Nijmegen Questionnaire in relation to the clinical diagnosis was 91% and the specificity 95%.

The Maastricht hypochondria scale (MEGAH) (37) assesses different components of hypochondria. Sixty-seven statements are divided into 5 scales; 'fear of own health' (min 12; max 60), 'general health fear' (min 16; max 80), 'illness belief' (min 7; max 35), 'confidence in doctors' (min 6; max 30) and 'search of medical information' (min 3; max 15). The sum of the first three subscales is a measure for the amount of hypochondria (min 35; max 175). The statements have to be answered on a five-point scale varying from 1; 'strongly agree' to 5; 'strongly disagree', whereby a lower score is less favourable.

Displeasure (min 10; max 30) and feelings of physical disability (min 12; max 36) can be assessed with subscales of the Heart Patients Psychological Questionnaire (HPPQ) (38). The subscales consist of respectively 10 and 12 items which can be rated on a three-point scale (yes/?/no). Validity and reliability for the Dutch population have proven to be sufficient (64).

The Fear Survey Schedule (FSS) (39-41) can be used to assess 'fear related to bodily injury, death and illness' and 'social anxiety'. The subscales consist of respectively 12 and 13 items which have to be rated on a five-point Likert scale (1 = not at all, 5 = extremely). Validity and reliability for the Dutch population have proven to be good (64).

By means of the Profile Of Mood States (POMS) (42) depression, anger, fatigue, vigour and tension can be measured. The subscales consist of respectively 8, 7, 6, 5 and 6 items which have to be rated on a 5-point Likert scale varying from 0 = not at all to 4 = extremely. Each item reflects a state of mood which might have occurred during the preceding days. The total score (0 to 128) of all items gives an indication of the patient's peevishness. Reliability in the Netherlands, has proven to be good (42).

# 5. Empirical psychological modelling of chest pain; a follow up study

*A.W. Serlie, H.J. Duivenvoorden, J. Passchier, F.J. ten Cate, J.W. Deckers, R.A.M. Erdman*

*(submitted)*

## 5.1 Abstract

In this follow-up study the psychological profiles of 39 patients with non-cardiac chest pain (NCA) and 33 patients with coronary artery disease (CAD) were assessed 1.6 years after the first consultation by their treating cardiologist. This was done in order to construct an empirical psychological model, which would be able to discriminate these two groups, after the diagnosis non-cardiac/cardiac was known.

Based of earlier findings, concerning the aetiology of non-cardiac chest pain, all patients completed questionnaires which were operationalisations of the constructs of relevance.

The non-cardiac patients were significantly younger than the cardiac ones. Additionally, the non-cardiac patients had higher levels of anxiety, fear for their own health and fear related to bodily injury, death and illness, but had less chest pain typical for angina pectoris, less vigour and had less confidence in doctors than cardiac patients. Logistic regression on the variables jointly, adjusted for age and gender, showed that hypochondriac fears for their own health, fears related to bodily injury, death and illness and emotional tension contributed significantly to the model for discriminating between both groups.

Consistent with earlier studies the results shows that even after having been assured that the chest pain complaints are not somatogenic, non-cardiac patients remain to display a higher level of psychological morbidity compared to cardiac patients.

## 5.2 Introduction

It is has been well documented in contemporary literature (1-7), that the prevalence of normal or minimally diseased coronary arteries in patients referred to the cardiology out-patient's clinic for chest pain is 30 percent. These non-cardiac chest pain patients are more often female, relatively young, frequently suffer from panic disorder, hyperventilate, are considered to be depressed and anxious and the prevalence of atypical chest pain is relatively high (1-5, 8-17).

Follow-up studies of non-cardiac patients have shown that the prospects of survival are normal, but that the chest pain complaints in many cases do not diminish and sometimes even increase (11, 18-23). Additionally, studies by Lantinga et al. (11) and Potts and Bass (7) showed that psychological morbidity remained high, with high levels of anxiety, depression and somatisation.

Most of the studies mentioned above only signal the differences between the cardiac and non-cardiac chest pain patients on the variables separately, but not quantitatively relate them to a model comprising variables with differential potential jointly.

In a previous baseline study, at the Rotterdam University Hospital, the psychological profiles of 98 patients were assessed after the first consultation by their treating cardiologist. Patients were unfamiliar with the fact whether their complaints were of a somatic nature. In that study the non-cardiac patients displayed substantially higher levels of interpersonal sensitivity, displeasure, fears related to bodily injury, death and illness, depression, fatigue and total mood disturbance. Vigour was lower in the NCA group. By means of a logistic regression analysis we were able to differentiate the chest pain patients as being either cardiac or non-cardiac respectively; the performance implied that 80% of the patients were correctly differentiated. This performance was established by typical chest pain, feelings of disability, fatigue, hypochondriac fears of one's own health and fears related to bodily injury, death and illness (17).

In the present study we report the psychological findings, of the two patient categories, 1.6 years after the initial visit to the cardiologist, and we will explore the differential qualities of these variables are for the same patients. This will be done by constructing a model to differentiate non-cardiac from cardiac patients, based on these psychological characteristics. Additionally, we will examine whether the high performance of the differentiation can be

maintained at follow up and which variables are sustained in the model, as the latter may have implications for treatment necessity.

## 5.3 Methods

### 5.3.1 Patients

Eligible for this study were all 98 patients who were included in the baseline study. The inclusion criteria for that study were: referral to the cardiology out-patient's clinic of the Rotterdam University Hospital 'Dijkzigt', for the first time, with chest pain as a chief complaint. The nature of the complaints had to be either cardiac or non-cardiac. Further inclusion criteria at baseline were: sufficient proficiency of the Dutch language, age over 18 or under 75 years, no prior history of coronary artery disease or other organic heart diseases, other somatic causes for their chest pain complaints or a history of psychiatric illness.

The final diagnosis for the baseline study was assessed after an average of 1.6 years. Once the final diagnosis had been determined, all 98 baseline patients were subsequently sent a letter informing them about the follow-up study. In this way the chance of a patient being misdiagnosed was kept to a minimum. The patients were requested to fill out questionnaires supplied. A pre-paid envelop was provided for returning the questionnaires. Furthermore, an effort was made to contact the patients after one week as to help with any problems encountered when filling-out the questionnaires and to request the patients to swiftly return the questionnaires.

In total 55 non-cardiac patients and 43 cardiac patients were eligible for the present study. Ten patients (10%) were unwilling to participate, eleven (11%) could not be contacted, five patients (5%) had moved or were abroad and one patient had completed less than half of the questionnaires. The proportion of non-participants was evenly distributed over both categories of patients. Consequently, the data of 72 ($n_{nca}$=39, $n_{cad}$=33) of the eligible patients could be used for statistical analysis.

### 5.3.2 Cardiological assessment

Present chest pain typical for angina was assessed by means of the Rose questionnaire (24). In this questionnaire patients were asked questions concerning their type of chest pain. Typical chest pain is defined present when

patients indicate having chest pain a) when walking or hurrying, b) reduction of the pain within ten minutes when resting and c) located at the sternum or left anterior chest and left arm.

Furthermore, the level of experienced chest pain was measured with a visual analogue scale (VAS). Patients were asked to indicate the intensity of their chest pain, at first consultation and pain experienced recently, by placing a cross on a 10 cm continuum. A cross to the far left (0 cm) meant no pain at all and to the far right (10 cm) meant unbearable pain.

### 5.3.3 General characteristics

Information was gathered on the patient's present marital and employment status, smoking habits and education level. Additionally, life events, in the past year, were registered using a shortened Dutch version of Paykel's life event scale (25). The five items involving the highest rates of stressfulness were classified as major life events. Major life events were: divorce; death of wife/husband, parent(s), offspring or good friend. Minor life events were: hospitalization of the subject or close family members; having offspring with a handicap; marriage; becoming unemployed/retirement/being declared medically unfit; becoming a parent; child not being promoted to the next grade; child starting school, changing school, getting married, leaving home; friend of child dying; removal.

### 5.3.4 Psychological assessment

On the basis of earlier findings, concerning the aetiology of non-cardiac chest pain (1-5, 8-12, 16), the following questionnaires were used at baseline as well as at follow-up, to operationalise the constructs of relevance.

The Hospital Anxiety Depression Scale (HAD) (26), was used to assess anxiety and depression. The questionnaire consists of 14 questions, half reflecting anxiety and half depression. The answer possibilities indicate the intensity of the given mood; the sum of the individual scores give an overall anxiety (min 0; max 21) and depression (min 0; max 21) score. Validity and reliability have been proven for British studies (2)

Psychopathology was measured with the General Health Questionnaire (GHQ-12). The twelve items of this self-rating questionnaire reflect a measure of severity of functional non-psychotic psychopathology. The questions relate to unusual or unpleasant psychological experiences. Patients are requested to

answer by indicating, on a four point scale, the difference between their present situation compared to their normal situation, choosing from 'none', 'no more than usual', 'more than usual' and 'a lot more than usual'. The total scores (min 0; max 12) were obtained using the conventional scoring (0-0-1-1) (27). Validity and reliability for the Dutch version have been demonstrated (28, 29).

The Symptom Checklist (SCL-90) (30) was used to assess agoraphobia (min 7; max 35; $\bar{x}_{norm}$ 8.4), anxiety (min 10; max 50; $\bar{x}_{norm}$ 13.9), depression (min 16; max 80; $\bar{x}_{norm}$ 22.5), somatisation (min 12; max 60; $\bar{x}_{norm}$ 17.8), obsessive compulsive behaviour (min 9; max 45; $\bar{x}_{norm}$ 13.7), interpersonal sensitivity (min 18; max 90; $\bar{x}_{norm}$ 25.6), hostility (min 6; max 30; $\bar{x}_{norm}$ 7.6), sleeping-problems (min 3; max 15; $\bar{x}_{norm}$ 4.9) and the total of all subscales, including the residual items; psychoneuroticism (min 90; max 450; $\bar{x}_{norm}$ 123.9). The SCL-90 is a widely used self-report questionnaire in medical research, to categorize and quantify psychological distress. Patients rate on a five-point Likert scale (1 = not at all, 5 = extremely) the degree of distress they have experienced in the preceding week, from each of 90 items. Validity and reliability have proven to be good for the Dutch population (31).

Hyperventilation was measured with the Nijmegen Questionnaire (NQ) (32). The questionnaire consists of 16 complaints whose frequency of occurrence can be indicated on a five-point Likert scale (never, rarely, sometimes, often and very frequently). The complaints relate to different systems; (a) cardiovascular e.g. 'palpitations'; (b) neurological, e.g. 'dizzy spells', tingling fingers'; (c) respiratory e.g. 'shortness of breath'; (d) gastro-intestinal, e.g. bloated abdominal sensation'; (e) psyche, e.g. 'tense' and 'anxious feeling'. Total scores can range from 0 to 64, whereby 0-20 is considered as probably no hyperventilation, 20-30 further observation is needed and more than 30 most certainly hyperventilation. In Van Dixhoorn and Duivenvoorden's study (32) the sensitivity of the Nijmegen Questionnaire in relation to the clinical diagnosis was 91% and the specificity 95%.

Hypochondria was assessed with the Maastricht hypochondria scale (MEGAH) (33). Sixty-seven statements are divided into 5 subscales; 'fear of own health' (min 12; max 60; < 40: hypochondriac fears of own health), 'general health fear' (min 16; max 80; < 40 hypochondriac general health fears), 'illness belief' (min 7; max 35; < 28 hypochondriac illness belief), 'confidence in doctors' (min 6; max 30) and 'search of medical information' (min 3; max 15). The sum of the first three subscales is a measure for the amount of hypochon-

dria (min 35; max 175; < 100: hypochondria according to DSM-III-R). The statements have to be answered on a five-point scale varying from 1; 'strongly agree' to 5; 'strongly disagree', whereby a lower score is less favourable.

Displeasure (min 10; max 30) and feelings disability (min 12; max 36) were assessed with subscales of the Heart Patients Psychological Questionnaire (HPPQ) (34). The subscales consist of respectively 10 and 12 items which can be rated on a three-point scale (yes/?/no). Validity and reliability for the Dutch population have proven to be sufficient (31).

Two subscales of the Fear Survey Schedule (FSS) (35-37) were used to assess 'fear for bodily injury' and 'social anxiety'. The subscales consist of respectively 12 and 13 items which have to be rated on a five-point Likert scale (1 = not at all, 5 = extremely). Validity and reliability for the Dutch population have proven to be good.

By means of the Profile Of Mood States (POMS) (38) depression, anger, fatigue, vigour and tension were measured. The subscales consist of respectively 8, 7, 6, 5 and 6 items which have to be rated on a 5-point Likert scale varying from 0 = not at all to 4 = extremely. Each item reflects a state of mood which might have occurred during the preceding days. The total score of all items gives an indication of the patient's peevishness. Reliability in the Netherlands, has proven to be good (38).

### 5.3.5 Statistical analysis

Before answering the research questions, missing data were estimated for variables of which the percentage missing was below 15%. No variables were disregarded, as the percentage missing did not exceed 15%. For estimating the values of the missing data the predicted mean matching method was used (39). Other variables were utilized as predictors for the missing variables. Regression analysis, with the procedure backwards elimination, was used for this purpose. Only predictor variables that were significant at 0.05 level were maintained in the regression model.

Nominal data such as gender and marital status were tested by means of $\chi^2$ statistic. A variable was defined as being statistically significant when $p < 0.05$.

For both the NCA and the CAD group the means including the 95% confidence intervals and the confidence intervals for the difference are presented. The statistical significance is defined as the 95% confidence interval of the

difference excluding the value 0.0 (40). The magnitude of the difference between the two groups of patients is calculated using Cohen's $\delta$ (41). The differences between the two groups were also formally tested by means of a oneway analysis of variance (42).

Furthermore, all psychological variables and typical chest pain were examined by means of a logistic regression analysis. With this multivariate modelling technique an estimation of the probability of being a non-cardiac patient can be made. Standardized values (i.e. z-scores) of the variables were used in the analyses, because the estimated regression coefficients ($\beta$) can then be considered as measures of relative importance. In the analyses the backward elimination procedure was used. Here too, only predictor variables that were significant at 0.05 level, were maintained in the model. We will present the estimated coefficients ($\beta$), the odds variable ($\exp\beta$), the standard error of $\beta$ (se $\beta$), as a measure of precision, and the 95% confidence intervals. The variables significantly contributing the differentiation between non-cardiac and cardiac chest pain were subsequently analyzed once again by means of a logistic regression analysis, using the enter method, to be able to adjust the model for age and gender.

Thereafter, a receiver-operator characteristic (ROC) curve was constructed for psychological characteristics adjusted for age and gender. The logistic model calculated the predicted probability of being a non-cardiac patient and subsequently sensitivity and specificity were calculated. In the ROC curve, the true-positive rate (sensitivity) is plotted against the false-positive rate (1 − specificity) and the discriminative ability of a test is shown by the position of the full curve: the farther upward and to the left the curve lies in the figure, the more optimal the test is. Thus, the area under the ROC-curve reflects the performance of the model, in a sense that a larger surface area reflects a higher performance (43).

Finally, the model was crossvalidated by randomly assigning patients into five strata, comprising the same odds non-cardiac/cardiac and male/female patients as the total group. A model was constructed based on four of these strata (training sample) and the probabilities of the fifth stratum were then estimated based on the constructed model (validation sample). This procedure was followed for all five possible strata. Subsequently, the estimated probabilities were compared with the probabilities of the model based on all patients, using a regression analysis.

## 5.4 Results

The general characteristics for both the non-cardiac and the cardiac patients can be found in Table 5.1. As can be seen, the non-cardiac patients were on average significantly younger than cardiac patients and their chest pain was less typical for angina pectoris. A significantly larger proportion of non-cardiac patients was engaged full time employment. On all the other general characteristics, including major and minor life events, the two patient categories did not differ significantly. It is noteworthy to mention that 35% of the non-cardiac and 32% of the cardiac patients perceived their chest pain to be the same or even more than at baseline.

The psychological characteristics of both patient categories can be found in Table 5.2. The NCA patients show significantly higher levels of HAD-anxiety and fears related to bodily injury, death and illness. They also show more hypochondriac anxiety related to their own health as indicated by a lower score on the MEGAH subscale. Finally, the non-cardiac patients have a significantly lower confidence in doctors than the cardiac patients and show less vigour. The effect size of the differentiating variables is moderate, as can be seen from an absolute Cohen's $\delta$ between 0.50 and 0.80 (41).

By means of the logistic regression method of analysis with backward elimination a quantitative model for the prediction of non-cardiac chest pain was constructed. Being cardiac (yes/no) was the criterion variable and typical chest pain and the psychological variables except the hypochondria index, were used as the predictor variables. Due to multicollinearity between general health fear and the hypochondria index, the hypochondria index was omitted, as this variable is a summation of three subscales of the MEGAH, and is therefore most likely redundant.

The logistic model showed that non-cardiac patients can be differentiated from cardiac patients by lower levels of typical chest pain, general health fear, disability and tension but higher levels of obsessive compulsive behaviour, fear for one's own health and fears related to bodily injury, illness and death. The overall correct classification of this model was 81.9%. Taking the prior probability of 54.2% into account, the model shows an improvement of 61%, compared to the prior probability.

**Table 5.1** *General characteristics of non-cardiac (NCA) and cardiac (CAD) patients*[*]

| | NCA | CAD) | Statistic | P value |
|---|---|---|---|---|
| Age (mean(±SD)) | 52.07 (10.5) | 64.82 (7.7) | F= 33.24 | ≪ 0.01 |
| Gender | | | | |
| male | 17 | 21 | $\chi^2$=2.13 | 0.14 |
| female | 22 | 12 | | |
| Marital status | | | | |
| partner | 33 | 27 | $\chi^2$=0.00 | 1.00 |
| single | 6 | 5 | | |
| Full time employment[**] | | | | |
| yes | 16 | 2 | $\chi^2$=9.47 | < 0.01 |
| no | 23 | 30 | | |
| Smoking | | | | |
| current | 9 | 8 | $\chi^2$=0.60 | 0.74 |
| ex-smoker | 17 | 16 | | |
| non-smoker | 13 | 8 | | |
| Education | | | | |
| Primary | 12 | 16 | $\chi^2$=2.80 | 0.25 |
| Secondary | 18 | 10 | | |
| Higher | 9 | 6 | | |
| Major life events | | | | |
| 0 | 29 | 29 | $\chi^2$=2.20 | 0.33 |
| 1 | 8 | 3 | | |
| 2 | 2 | 1 | | |
| Minor life events | | | | |
| 0 | 20 | 14 | $\chi^2$=0.56 | 0.75 |
| 1 | 11 | 11 | | |
| > 1 | 8 | 8 | | |
| Typical chest pain | | | | |
| yes | 2 | 13 | $\chi^2$=10.73 | ≪ 0.01 |
| no | 37 | 20 | | |
| Chest pain | | | | |
| same or more | 12 | 10 | $\chi^2$=0.28 | 0.87 |
| less | 17 | 16 | | |
| no pain | 5 | 5 | | |

* For some variables N will not always add up to 72, due to missing values

** More than 32 hours a week

**Table 5.2** *Psychological characteristics of non-cardiac (NCA) and cardiac (CAD) patients*

| Determinant | Non-cardiac | | Cardiac | | Difference | | |
|---|---|---|---|---|---|---|---|
| | $x_{nca}$ | 95% CI | $x_{cad}$ | 95% CI | Cohen's $\delta$ | 95% CI | P value |
| **HAD** | | | | | | | |
| Anxiety | 7.38 | 5.86 ; 8.90 | 5.22 | 3.88 ; 6.56 | 0.50 | 0.10 ; 4.22 | <0.05 |
| Depression | 6.15 | 4.85 ; 7.45 | 4.52 | 3.22 ; 5.82 | 0.42 | -0.24 ; 3.50 | 0.08 |
| **GHQ** | | | | | | | |
| Psychopathology | 3.67 | 2.61 ; 4.73 | 2.33 | 1.19 ; 3.47 | 0.41 | -0.22 ; 2.90 | 0.09 |
| **SCL-90** | | | | | | | |
| Agoraphobia | 9.44 | 7.52 ; 11.36 | 8.18 | 7.02 ; 9.34 | 0.26 | -1.07; 3.59 | 0.28 |
| Anxiety | 17.09 | 14.59 ; 19.59 | 15.36 | 13.26 ; 17.46 | 0.25 | -1.60; 5.06 | 0.30 |
| Depression | 26.46 | 22.70 ; 30.22 | 23.34 | 14.42 ; 32.26 | 0.30 | -1.77; 8.01 | 0.21 |
| Somatization | 24.59 | 21.29 ; 27.89 | 20.94 | 18.44 ; 23.44 | 0.41 | -0.61; 7.91 | 0.09 |
| Obses. compuls | 16.47 | 14.33 ; 18.61 | 14.15 | 12.47 ; 15.83 | 0.39 | -0.48; 5.12 | 0.10 |
| Interp. sensitiv. | 25.73 | 22.47 ; 28.99 | 23.04 | 21.02 ; 25.06 | 0.32 | -1.32; 6.70 | 0.18 |
| Hostility | 7.98 | 7.00 ; 8.96 | 7.97 | 7.03 ; 8.91 | 0.00 | -1.36; 1.38 | 0.98 |
| Sleepproblems | 6.18 | 5.22 ; 7.14 | 5.36 | 4.34 ; 6.38 | 0.28 | -0.58; 2.22 | 0.25 |
| Psychoneurot. | 145.84 | 127.92;163.76 | 130.17 | 118.13;142.21 | 0.35 | -5.36; 36.70 | 0.17 |
| **NQ** | | | | | | | |
| Hypervent | 20.01 | 16.13 ; 23.89 | 16.77 | 13.67 ; 19.87 | 0.30 | -1.85; 8.33 | 0.21 |
| **MEGAH** | | | | | | | |
| Fear own health | 45.07 | 41.37 ; 48.77 | 51.42 | 48.12 ; 54.72 | -0.60 | -11.39; -1.31 | <0.05 |
| Med informat | 12.44 | 11.50 ; 13.38 | 11.48 | 10.12 ; 12.84 | 0.28 | -0.65; 2.57 | 0.32 |
| Conf in doctors | 19.22 | 17.40 ; 21.04 | 23.19 | 21.65 ; 24.73 | -0.78 | -6.40; -1.54 | ≪0.01 |
| Illness belief | 25.56 | 23.36 ; 27.76 | 27.10 | 25.08 ; 29.12 | -0.24 | -4.58; 1.50 | 0.32 |
| Gen health | 41.53 | 36.97 ; 46.09 | 39.77 | 35.51 ; 44.03 | 0.13 | -4.56; 8.08 | 0.58 |
| Hypoch index | 111.73 | 103.21;120.25 | 118.80 | 111.06 ; 126.54 | -0.29 | -18.76; 4.62 | 0.23 |
| **HPPQ** | | | | | | | |
| Disability | 24.13 | 21.75 ; 26.51 | 26.02 | 23.78 ; 28.26 | -0.27 | -5.18; 1.40 | 0.25 |
| Displeasure | 15.25 | 13.91 ; 16.59 | 13.81 | 12.31 ; 15.31 | 0.34 | -0.56; 3.44 | 0.16 |
| **FSS** | | | | | | | |
| Fear bod. injury | 21.55 | 18.97 ; 24.13 | 17.47 | 15.75 ; 19.19 | 0.60 | 0.87; 7.29 | <0.05 |
| Social anxiety | 21.54 | 19.14 ; 23.94 | 20.03 | 18.03 ; 22.03 | 0.22 | -1.68; 4.70 | 0.35 |
| **POMS** | | | | | | | |
| Depression | 4.54 | 2.24 ; 6.84 | 2.27 | 0.61 ; 3.93 | 0.37 | -0.67; 5.21 | 0.13 |
| Anger | 4.00 | 2.22 ; 5.78 | 3.21 | 1.35 ; 5.07 | 0.14 | -1.81; 3.39 | 0.54 |
| Fatigue | 7.18 | 4.96 ; 9.40 | 4.39 | 2.31 ; 6.47 | 0.43 | -0.30; 5.88 | 0.08 |
| Vigour | 9.15 | 7.69 ; 10.61 | 11.67 | 10.31 ; 13.03 | -0.60 | -4.53; -0.51 | <0.05 |
| Tension | 5.77 | 3.81 ; 7.73 | 4.61 | 2.79 ; 6.43 | 0.20 | -1.55; 3.87 | 0.40 |
| Total mood dist | 32.33 | 24.31 ; 40.35 | 22.82 | 15.96 ; 29.96 | 0.42 | -1.26; 20.28 | 0.08 |

**Table 5.3** *Differential qualities for psychological determinants unadjusted and adjusted for gender and age*

| Determinant | β | | expβ | | SE β | | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| | unadj | adj | unadj | adj | unadj | adj | unadjusted | adjusted |
| Typical Angina | -1.37 | -1.33 | 0.25 | 0.26 | 0.53 | 0.73 | 0.09 ; 0.73* | 0.06 ; 1.14 |
| Obses. compuls. | 1.29 | 1.01 | 3.63 | 2.75 | 0.55 | 0.74 | 1.21 ; 10.91* | 0.63 ; 12.06 |
| Fear own health | -1.82 | -2.20 | 0.16 | 0.11 | 0.64 | 0.84 | 0.05 ; 0.58* | 0.02 ; 0.59* |
| Gen. health fear | 0.95 | 0.84 | 2.59 | 2.32 | 0.43 | 0.54 | 1.09 ; 6.11* | 0.79 ; 6.82 |
| Disability | -0.88 | -0.72 | 0.41 | 0.49 | 0.45 | 0.63 | 0.17 ; 1.02* | 0.14 ; 1.72 |
| Fear of bod Injury | 1.13 | 1.70 | 3.10 | 5.47 | 0.43 | 0.63 | 1.31 ; 7.32* | 1.55 ; 19.30* |
| Tension | -1.47 | -2.48 | 0.23 | 0.08 | 0.66 | 1.03 | 0.06 ; 0.86* | 0.01 ; 0.66* |

When adjusted for age and gender, only fear for one's own health, fear related to bodily injury, death and illness and tension significantly contributed to the predictability of non-cardiac chest pain (see Table 5.3). The overall correct classification of the adjusted model was 75%.

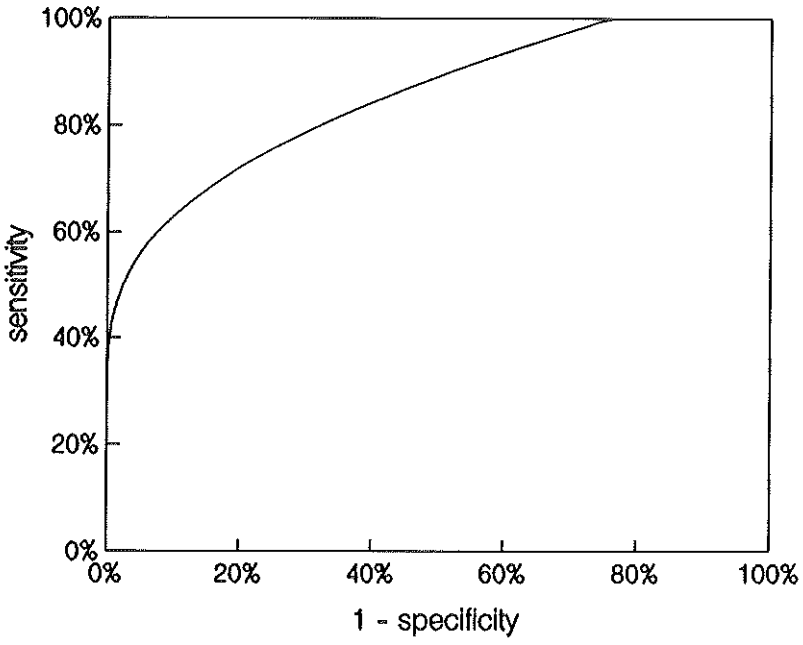
In Figure 5.1 the ROC-curve for the adjusted model is shown. The area under the adjusted ROC-curve is 0.80 (95% CI: 0.73 to 0.88), indicating a high performance.

Figure 5.2 shows the difference between the predicted probability acquired by crossvalidation and the predicted probability derived from the final logistic model. The small regression coefficient ($\beta = -0.04$) and intercept (-0.02) of the regression line, both statistically insignificant, indicate that the constructed model is stable.

## 5.5 Discussion

Consistent with earlier studies (7, 11) the present study shows that even after having been assured that the chest pain complaints are not somatogenic, non-cardiac patients remain to display a higher level of psychological morbidity compared to cardiac patients. At baseline the non-cardiac patient had more fears related to bodily injury, death and illness, showed more displeasure, depression and had higher levels of mood disturbance than the cardiac patients (17). At follow-up, these non-cardiac patients are significantly more anxious than cardiac patients, as demonstrated by higher anxiety on the HAD, higher levels of hypochondriac fears for their own health and more fears related to

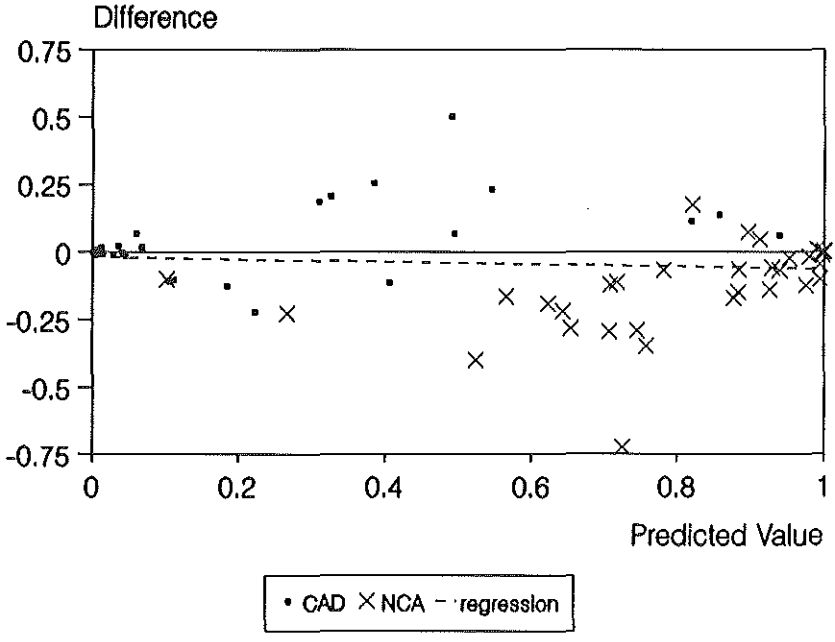
**Figure 5.1** *Receiver Operator Characteristic Curve of the model adjusted for age and gender*




bodily injury, death and illness. These findings may be surprising as one would expect that patients for whom it has been objectively demonstrated that there is no somatic cause for their complaints, would be relieved. Furthermore, one would expect the cardiac patients to be more anxious when he or she has been told that he or she suffers from a cardiac disease. Perhaps this discrepancy can be explained by the fact that contrary to non-cardiac patients, cardiac patients do not have the uncertainty about the reasons for their chest pain. This positive correlation between uncertainty and anxiety can, for instance, also be found in cancer research (e.g. (44)). On top of that, cardiac patient, generally, receive adequate medical treatment for their chest pain, which can relieve the pain when present. Tibbling (45), for that matter, suggested that placebo treatment in non-cardiac patients might be very useful.

The logistic model found at baseline could correctly classify 80% of the patients. This was achieved on the basis of the variables typical chest pain, disability, fatigue, fear for one's own health and fears related to bodily injury, death and illness. The performance of the logistic model found in the present study is similar as it can correctly classify 75% of the patients as being non-

**Figure 5.2** *Predicted probability of being a NCA patient set against the difference between the predicted value of the final model and the crossvalidated model for both the CAD (▪) and the NCA (×) patients.*




cardiac or cardiac. The model again entails the variables fear for one's own health and fears related to bodily injury, death and illness and additionally emotional tension. Both models reflect anxiety being manifest in the non-cardiac patients. The importance of anxiety has been well documented in previous studies (1, 2, 4, 5, 10-12, 16), in which it was shown that on various anxiety questionnaires, non-cardiac patients had higher levels of anxiety than cardiac patient did. Eifert (46) even went as far as to advocate that non-cardiac chest pain should be considered as a phobic anxiety disorder rather than a non-organic chest pain problem. Moreover, he gave various reasons why non-cardiac chest pain fits in with the DSM-III criteria for a phobic anxiety disorder.

This study shows that Dutch non-cardiac patients are psychologically comparable to British, American and German non-cardiac patients, and that simple reassurance that 'there is nothing wrong' does not suffice in diminishing feelings of anxiety long after the correct diagnosis is known. Adequate psychological or psychiatric treatment may therefore be in order. This becomes even

more poignant, when one realizes that various studies have shown that positive treatment results can be accomplished relatively easily in a number of cases by cognitive behavioral psychotherapy (47, 48). Perhaps, because of the lower confidence in doctors displayed by the non-cardiac patients this will motivate treating cardiologists to refer non-cardiac patients to experienced psychologists or psychiatrists, for appropriate treatment, more readily.

## 5.6 References


1. Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med. 1984; 14(1): 51-61.
2. Channer KS, Papouchado M, James MA, Rees JR. Anxiety and depression in patients with chest pain referred for exercise testing. Lancet 1985; 2(8459): 820-823.
3. Beitman BD, Basha I, Flaker G, DeRosear L, Mukerji V, Lamberti JW. Major depression in cardiology chest pain patients without coronary artery disease and with panic disorder. J Affective Disord 1987; 13(1): 51-59.
4. Katon W, Hall ML, Russo J, et al. Chest pain: relationship of psychiatric illness to coronary arteriographic results. Am J Med 1988; 84(1): 1-9.
5. Cormier LE, Katon W, Russo J, Hollifield M, Hall ML, Vitaliano PP. Chest pain with negative cardiac diagnostic studies. Relationship to psychiatric illness. J Nerv Ment Dis 1988; 176(6): 351-358.
6. Eifert GH. Cardiophobia: An anxiety disorder in its own right? Special Issue: Research in anxiety and fear. Behav Change 1991; 8(3): 100-116.
7. Potts SG, Bass CM. Psychological morbidity in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. Psych Med 1995; 25(2): 339-347.
8. Costa PT, Zonderman AB, Engel BT, Baile WF, Brimlow DL, Brinker J. The relation of chest pain symptoms to angiographic findings of coronary artery stenosis and neuroticism. Psychosom Med. 1985; 47(3): 285-293.
9. Papanicolaou MN, Califf RM, Hlatky MA, et al. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. Am J Cardiol 1986; 58(13): 1181-1187.
10. Bass C, Chambers JB, Kiff P, Cooper D, Gardner WN. Panic anxiety and hyperventilation in patients with chest pain: a controlled study. Q J Med 1988; 69(260): 949-959.

11. Lantinga LJ, Sprafkin RP, McCroskery JH, Baker MT, Warner RA, Hill NE. One-year psychosocial follow-up of patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1988; 62(4): 209-213.
12. Herrmann C, Scholz KH, Kreuzer H. [Psychologic screening of patients of a cardiologic acute care clinic with the German version of the Hospital Anxiety and Depression Scale] Psychologisches Screening von Patienten einer kardiologischen Akutklinik mt einer deutchen Fassung der "Hospital Anxiety and Depression" (HAD)-Skala. Psychother Psychosom Med Psychol. 1991; 41(2): 83-92.
13. Alexander PJ, Prabhu SG, Krishnamoorthy ES, Halkatti PC. Mental disorders in patients with noncardiac chest pain. Acta Psychiatr Scan 1994; 89(5): 291-293.
14. Mayou R, Bryant B, Forfar C, Clark D. Non-cardiac chest pain and benign palpitations in the cardiac clinic. Br Heart J 1994; 72: 548-553.
15. Serlie AW, Erdman RAM, Passchier J, Trijsburg RW, Ten Cate FJ. Psychological aspects of non-cardiac chest pain. Psychother Psychosom 1995; 64: 62-73.
16. Serlie AW, Duivenvoorden HJ, Passchier J, Ten Cate FJ, Deckers JW, Erdman RAM. Empirical psychological modelling of chest pain; a comparative study. J Psychosom Res (in press).
17. Serlie AW, Duivenvoorden HJ, Passchier J, Ten Cate FJ, Deckers JW, Erdman RAM. Empirical psychological modelling of chest pain; a cross--sectional study. submitted.
18. Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary arteriograms: a follow-up study of functional status. N Eng J Med 1980; 303(22): 1249-52.
19. Isner JM, Salem DN, Banas JS Jr., Levine HJ. Long-term clinical course of patients with normal coronary arteriography: Follow-up study of 121 patients with normal or nearly normal coronary arteriograms. Am Heart J 1981; 102: 645-653.
20. Moreyra AE, McGough WE, Hosler M, Kostis JB. Clinical improvement of patients with chest pain and normal coronary arteries after coronary arteriography: The possible role of hyperventilation syndrome. Int J Cardiol 1982; 2: 306-308.
21. Bass C, Jackson G. Angina with normal coronary arteriograms. Clinical status at one year. Arch Mal Coeur Vaiss. 1983; 76: 237-45.
22. Wielgosz AT, Fletcher RH, McCants CB, McKinnis RA, Haney TL, Williams RB. Unimproved chest pain in patients with minimal or no coronary disease: a behavioral phenomenon. Am Heart J 1984; 108(1): 67-72.

23. Van Dorpe A, Piessens J, Willems JL, De Geest H. Unexplained chest pain with normal coronary arteriograms. A follow-up study. Cardiology. 1987; 74(6): 436-443.
24. Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. Geneva: World health organization, 1982. .
25. Paykel ES, Prusoff BA, Uhlenhuth EH. Scaling of life events. Arch Gen Psychiat 1971; 25: 340-347.
26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67(6): 361-370.
27. Goldberg DP. The detection of psychiatric illness by questionnaire. Oxford: Oxford university press, 1972. (vol 21).
28. Ormel J, Koeter MW, Van den Brink W, Giel R. Concurrent validity of GHQ-28 and PSE as measures of change. Psychol Med 1989; 19(4): 1007-1013.
29. Ormel J, Koeter MW, Van den Brink W. Measuring change with the General Health Questionnaire (GHQ). The problem of retest effects. Soc Psychiatry Psychiatr Epidemiol 1989; 24(5): 227-232.
30. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. Br J Psychiatr 1976; 128: 280-289.
31. Evers A, Van Vliet-Mulder JC, Ter Laak J. [Documentation of tests and testreseach in the Netherlands] Documentatie van tests en testresearch in Nederland. Assen: Van Gorchum, 1992. .
32. Van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. J Psychosom Res. 1985; 29(2): 199-206.
33. Schmidt AJ, Lousberg R. [Health-attitude and hypochondrias: Development of the MEGAH-scale] Gezondheidsattitude en hypochondrie. Ontwikkeling van de Maastrichter eigen gezondheidsattitude en hypochondrie--schaal. Gedrag en Gezondheid 1993; 21(2): 84-94.
34. Erdman RAM, Duivenvoorden HJ, Verhage F, Kazemier M, Hugenholtz PG. Predictability of beneficial effects in cardiac rehabilitation: a randomised clinical trial of psychological variables. J Cardiopulm Rehabil 1986; 6: 206-213.
35. Wolpe J, Lang PJ. A fear survey schedule for use in behaviour therapy. Behav Res Ther 1964; 2: 27-30.
36. Arrindell WA. Dimensional structure and psychopathology correlates of the Fear Survey Schedule (FSS-III) in a phobic population: A factorial definition of agoraphobia. Behav Res Ther 1980; 18(4): 229-242.
37. Arrindell WA, Zwaan EJ. [Phobic factors on the AZU-Fear Questionnaire (AZUV) and Wolpe and Lang's Fear Survey Schedule (FSS-III)] Fobische dimensies, de AZU-Vreesvragenlijst (AZUV) en Wolpe en Lang's Fear Survey Schedule (FSS-III). Ned Tijdschr Psychol 1982; 37(4): 225-239.

38. Wald FDM, Mellenbergh GJ. [The shortened version of the Dutch translation of the Profile of Mood States] De verkorte versie van de Nederlandse vertaling van de Profile of Mood States. Ned Tijdschr Psychol 1990; 45: 86-90.
39. Little RJA. Missing-data adjustments in large surveys. J Bus Econ Stat 1988; 6(3): 287-296.
40. Gardner MJ, Altman DG. Statistics with Confidence: confidence intervals and statistical guidelines. London: British Medical Journal, 1989. .
41. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale: Erlbaum, 1988. .
42. SPSS-Inc. Statistical package for the social sciences. Chicago, 1990. .
43. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143(1): 29-36.
44. Wong CA, Bramwell L. Uncertainty and anxiety after mastectomy for breast cancer. Cancer Nurs 1992; 15(5): 363-371.
45. Tibbling L. Issues in the treatment of noncardiac chest pain. Am J Med. 1992; 92(5A): 84.
46. Eifert GH. Cardiophobia: a paradigmatic behavioural model of heart-focused anxiety and non-anginal chest pain. Behav Res Ther 1992; 30(4): 329-345.
47. Klimes I, Mayou RA, Pearce MJ, Coles L, Fagg JR. Psychological treatment for atypical non-cardiac chest pain: A controlled evaluation. Psychol Med 1990; 20(3): 605-611.
48. Nutzinger DO, Cayiroglu S, Grünberger J, Kieffer W, Zapotczky HG. Prognosis of cardiac phobia. Psychopathology 1990; 23: 63-72.

# 6. Empirical psychological modelling of chest pain

*A.W. Serlie, H.J. Duivenvoorden, J. Passchier, F.J. ten Cate, J.W. Deckers, R.A.M. Erdman*

*(submitted)*

## 6.1 Abstract

In this study we examined how age, anxiety, depression and somatisation are related to hyperventilation, a main discriminating variable for chest pain patients with either normal coronary arteries or with coronary artery disease. The data were collected by questionnaires completed by 67 patients in the non-cardiac and 47 patients in the cardiac group. We developed a structural model for both chest pain groups, using the LISREL program. The results showed, for both groups, a good fit of the constructed model to the data. For the non-cardiac group anxiety and somatisation had a direct effect on hyperventilation. Anxiety indirectly effected hyperventilation through depression and somatisation. Both age and depression had a direct and an indirect effect through somatisation. For the cardiac group hyperventilation was not effected by any variables, although anxiety and depression were directly related to somatisation.

## 6.2 Introduction

Chest pain without a clear somatic cause has intrigued the medical and psychological profession for many decades and has been known under various labels, corresponding with the reasons thought to be underlying the disorder (1). Back in the eighteen sixties Hartstone (2) and Stillé (3) were among the first pioneers researching the disorder, observing the conditions among soldiers. The ailment was labelled "muscular exhaustion of the heart" as it was ascribed to the stress of the military campaigns, with great and prolonged exertion, together with the deprivation of rest, food and clean water. Lewis (4) called the disorder "effort syndrome" as he believed that all the clinical features were those normally produced by effort, but in the affected soldiers occurred on very

slight effort. During the first world war the disorder was labelled "neurocirculatory asthenia" as a group of military physicians did not accept the term effort syndrome and did not want to include the term "heart" because of its psychological effect (5). In most recent literature, however, the disorder has been labelled cardiac neurosis, cardiophobia or just simply non-cardiac chest pain (6-11). Most of these studies have shown that the prevalence of normal or minimally diseased coronary arteries in patients with such chest pain is approximately 30 percent. These non-cardiac chest pain patients are relatively young, more often female, suffer from panic disorder, hyperventilate, are considered depressed and anxious and have a higher prevalence of atypical chest pain (6-10, 12-18).

Although the prospects of survival for these patients are favourable (11, 13, 15, 19-27), patients' symptoms do tend to persist or even increase over the years. Adequate treatment of these non-cardiac patients is therefore imperative. In order to be able to appropriately treat these patients it is, however, of relevance to understand the mechanisms underlying the disorder. In a previous study (28) it was shown that hyperventilation and anxiety were the foremost characteristics which could differentiate well between cardiac and non-cardiac chest pain patients. These findings were consistent with the results mentioned in earlier studies (14, 29-35), in which relatively more non-cardiac patients were found to suffer from hyperventilation and anxiety disorders than cardiac patients. Moreyra et al. (34), for instance, found that of a group of 40 non-cardiac patients 91% of the women and 66% of the men suffered from hyperventilation. In line with these findings, the results from a study by Bass et al. (14) suggested that hyperventilation might be one of the important mechanisms involved in the production of non-cardiac chest pain. In their study of chest pain, 26% of the anxious or depressed patients suffered from hyperventilation. Almost half the patients with elevated anxiety and depression scores were hypocapnic at rest. In addition, patients with panic anxiety reported significantly more symptoms of breathlessness and other hyperventilation-related somatic complaints and developed hypocapnia on exercise more frequently than those without panic.

Having established that hyperventilation appears to play a significant role in non-cardiac chest pain, the objective of the present study was to investigate, in detail, the kind of relationship between psychological variables which were found related to chest pain and hyperventilation for both cardiac and non-

cardiac chest pain patients. In doing this, we attempted to model this relationship quantitatively for both patient groups, using the LISREL technique.

## 6.3 Methods

### 6.3.1 Subjects

Eligible for this study were patients who had been referred to the cardiology out-patients' clinic of the Rotterdam University Hospital, for the first time, from March 1991 up to January 1993, with chest pain as a chief complaint. Exclusion criteria were 1) insufficient proficiency of the Dutch language, 2) age under 18 or over 75 years, 3) a history of psychiatric illness and 4) other medical complications or cardiac events, such as myocardial infarction or by-pass surgery, having occurred during the time of referral and the onset on the study.

Patients meeting the criteria, were selected from medical records available at the Thoraxcentre of the Rotterdam University Hospital. All selected patients had undergone extensive cardiological testing in order to assess whether the chest pain was of a somatic nature.

In total 163 patients were eligible for this study, 96 in the non-cardiac group (NCA) and 67 in the group with coronary artery disease (CAD). After elimination of patients unwilling to participate ($n_{nca}=26$; $n_{cad}=15$) or of patients who had completed less than 50% of the subscales ($n_{nca}=3$; $n_{cad}=5$) a total of 67 NCA patients (29 men, 38 women; mean age 48.5 yrs, SD 12.0) and 47 CAD patients (36 men, 11 women; mean age 60.7 yrs, SD 9.0), were utilisable for statistical analysis.

### 6.3.2 Procedure

This study was part of a larger study into the role of psychological variables related to non-cardiac chest pain. Patients were sent a letter by the research group, informing them about the study. After one week they were phoned by the first author (A.S.) to make an appointment at the cardiology out-patients' clinic, in order to fill out psychological questionnaires, which took around one hour. These appointments took place approximately one week later.

### 6.3.3 Psychological assessment

Based on earlier findings, concerning the aetiology of non-cardiac chest pain (6-10, 12-16), we measured anxiety, depression, somatisation and hyperventilation, assessed by the following questionnaires.

Three subscales of the Symptom Checklist (SCL-90) (36) were used to assess anxiety (min 10; max 50), depression (min 16; max 80) and somatisation (min 12; max 60). Patients rate on a five-point Likert scale (1 = not at all, 5 = extremely) the degree of distress they have experienced in the preceding week. Validity and reliability have proven to be good for the Dutch population (37).

Hyperventilation was measured with the Nijmegen Questionnaire (NQ) (38). The questionnaire comprises 16 complaints whose frequency of occurrence can be indicated on a five-point Likert scale (never, rarely, sometimes, often and very frequently). The complaints relate to different systems; (a) cardiovascular e.g. 'palpitations'; (b) neurological, e.g. 'dizzy spells', tingling fingers'; (c) respiratory e.g. 'shortness of breath'; (d) gastro-intestinal, e.g. bloated abdominal sensation'; (e) psyche, e.g. 'tense' or 'anxious feeling'. Total scores can range from 0 to 64, whereby a score of 23 can differentiate well between patients with and without hyperventilation. In Van Dixhoorn and Duivenvoorden's study (38) the sensitivity of the Nijmegen Questionnaire in relation to the clinical diagnosis was 91% and the specificity 95%, indicating a high performance.

### 6.3.4 Statistical analysis

For both the NCA and the CAD group the levels including the 95% confidence intervals are presented. In addition the magnitude of the difference between the two groups of patients is calculated using Cohen's $\delta$ (39). The statistical significance is defined as whether the 95% confidence interval of the difference includes the value 0.0 or not (40).

The differences between the two groups for age, anxiety, depression, somatisation and hyperventilation were also assessed by means of a oneway analysis of variance (SPSS/PC (41).

The main aim of this study was to build a model in which hyperventilation as the response variable (in LISREL terms the endogenous variable), was to be estimated optimally by the predictor variables age, and the three psychological variables anxiety, depression and somatisation (in LISREL terms the exogenous

variables; see figure 6.1 and 6.2 for a visualisation). The measurement model was easily constructed because the reliability coefficients were already known. The next step was to try to identify and specify the structural model.

As indices for the quality of the ultimate model fit to the data the following performance measures were used: 1) chi-square ($\chi^2$) testing of the model fit between the hypothetical model and the empirical data (i.e. $p > 0.05$); 2) two measures of adequacy of the model, namely goodness-of-fit index (GFI) and adjusted goodness-of-fit index (AGFI); 3) root mean square of standardized residuals; 4) standard errors and t-values for the individual parameters, and 5) modification indices. In case of rival models the most parsimonious one was chosen.

Because we had no independent sample, the cross-validation was done by computing the Cudeck and Browne index (42) for each model. This validation index is a measure of discrepancy between the fitted correlation matrix in the calibration sample and the correlation matrix of the validation sample. The model with the smallest validation index is expected to be the most stable.

Initially we specified a structural model on the basis of the idea that the psychological variables and age are directly related to hyperventilation as the endogenous variable (28). The second step was that we estimated the measurement model for each construct separately and then for the constructs jointly. For each model estimated in step 2 the fit was evaluated. For each model estimated, if this step lead to a modification of the model, the last step was repeated. The path coefficients are derived from standardised variables and are actually regression coefficients. The amount of variance explained by direct and indirect paths together is represented by $R^2$ which can theoretically vary from 0.0 (no variance explained at all) to 1.0 (all variance explained)

The analyses for constructing the structural model were conducted with the LISREL8 (43) program.

## 6.4 Results

The general characteristics of the two patient groups are depicted in Table 6.1. Consistent with findings in earlier studies (6-10, 12-16), the patients in the non-cardiac group were significantly younger ($p<0.01$), more often female ($p<0.01$) and single ($p<0.05$).

**Table 6.1** *Demographic characteristics of non-cardiac and cardiac patients*

| | NCA (N=67) | CAD (N=47) | P |
|---|---|---|---|
| Age (mean±S.D.) | 48.5 (12.0) | 60.6 (9.0) | <0.01 |
| Gender (male:female) | 29:38 | 36:11 | <0.01* |
| Marital status (partner:single) | 45:22 | 43:4 | <0.05† |

* $\chi^2=11.19$, df=1
† $\chi^2=7.95$, df=1

In Table 6.2 the psychological characteristics for both groups can be found. As can be seen there is a significant difference between the two groups for anxiety ($F(1,112)=9.44$; $p<0.01$), somatisation ($F(1,112)=8.54$; $p<0.01$) and hyperventilation ($F(1,112)=16.64$; $p<0.01$). The higher depression score of the non-cardiac group was statistically not significant ($F(1,112)=3.60$; $p=$ns).

**Table 6.2** *Psychological characteristics of non-cardiac vs cardiac patients*

| Determinant | Non-cardiac | | Cardiac | | Difference | | |
|---|---|---|---|---|---|---|---|
| | $\bar{x}$ | 95% CI | $\bar{x}$ | 95% CI | Cohen $\delta$ | 95% CI | P |
| Anxiety | 18.32 | 16.60;20.00 | 14.79 | 13.45;16.13 | 0.58 | 1.23;5.83 | < 0.01 |
| Depression | 26.82 | 24.50;29.18 | 23.62 | 21.42;25.82 | 0.36 | -0.16;6.56 | < 0.07 |
| Somatisation | 25.32 | 23.20;27.46 | 20.96 | 19.10;22.82 | 0.56 | 1.38;7.34 | < 0.01 |
| Hypervent. | 22.34 | 19.70;24.94 | 14.61 | 12.01;17.21 | 0.78 | 3.93;11.53 | < 0.01 |

For the structural model building, pearson correlations for both the cardiac and the non-cardiac group were used. Tables 6.3 and 6.4 show, for both the NCA and the CAD group, the observed correlations and the correlations fitted by the constructed model. As can be seen the observed and the fitted correlation are almost identical.

LISREL analysis on the correlation data of the non-cardiac group produced a model with its respective path coefficients and squared multiple correlation as shown in Figure 6.1. The goodness-of-fit test yielded a $\chi^2$-square of 1.77 (**df**=2, $p=0.41$), a goodness-of-fit index of 0.99 and an adjusted goodness-of-fit index of 0.92. The standardized root mean square residual was 0.03 and the

expected cross-validation index 0.42. These indicators suggest a good fit for the constructed model. A large amount of variance ($R^2$=0.90) of hyperventilation

**Table 6.3** *Correlation matrix for the NCA group; the upper half of the triangle, including the main diagonal depicts the fitted correlation matrix (italic), the lower half the observed correlation.*

| | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| 1. | Hyperventilation | *0.96* | *0.75* | *0.55* | *0.48* | *- 0.04* |
| 2. | Somatic | 0.77** | *1.00* | *0.44* | *0.55* | *0.19* |
| 3. | Anxiety | 0.60** | 0.51** | *1.00* | *0.72* | *- 0.07* |
| 4. | Depression | 0.47** | 0.53** | 0.71** | *1.00* | *- 0.06* |
| 5. | Age | - 0.04 | 0.18 | - 0.06 | - 0.08 | *1.00* |

two-tailed significance : *p <0.01 **p <0.001

**Table 6.4** *Correlation matrix for the CAD group; the upper half of the triangle, including the main diagonal, depicts the fitted correlation matrix (italic), the lower half the observed correlation*

| | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| 1. | Hyperventilation | *1.00* | *0.76* | *0.57* | *0.46* | *- 0.13* |
| 2. | Somatic | 0.76** | *0.99* | *0.61* | *0.49* | *- 0.14* |
| 3. | Anxiety | 0.57** | 0.59** | *1.00* | *0.37* | *- 0.10* |
| 4. | Depression | 0.46* | 0.46* | 0.49** | *1.00* | *- 0.08* |
| 5. | Age | - 0.12 | -0.14 | - 0.11 | -0.05 | *1.00* |

two-tailed significance : *p <0.01 ** p <0.001

was accounted for by the hypothesized relationships of this model. As can been seen from Figure 6.1, somatisation (0.94), anxiety (0.55), depression (-0.48) and age (-0.23) are directly related to hyperventilation. Next to the direct effects there are also indirect effects which are computed by multiplying the various pathcoefficients. Anxiety has an indirect (0.10) effect on hyperventilation through depression and somatisation. Depression has an indirect (0.60) effect on hyperventilation through somatisation. Finally, age has an indirect

effect (0.23) on hyperventilation through somatisation. As can be seen from Table 6.5, where direct, indirect and total effects on hyperventilation are depicted for all contributing variables, it is mainly anxiety (0.65) and somatisation (0.94) that are related highly to hyperventilation.

**Figure 6.1** *Structural model of chest pain for the non-cardiac patients (N=67; $\chi^2$=1.77; goodness-of-fit (GFI)= 0.99; adjusted goodness-of-fit index (AGFI)= 0.92)*

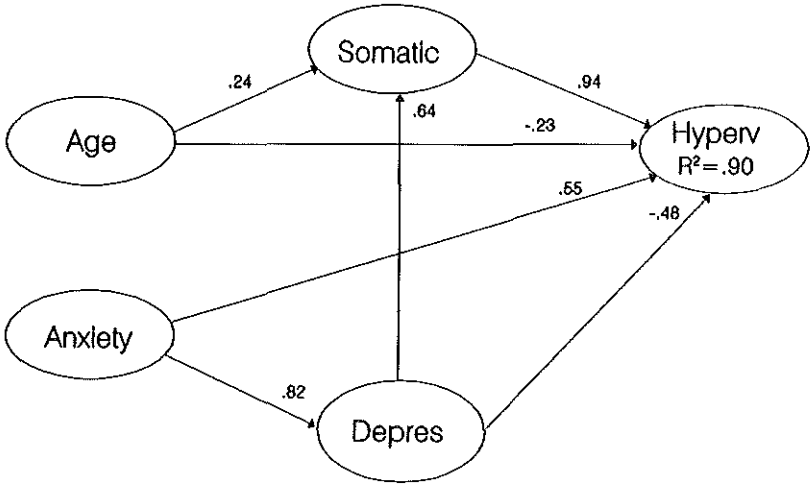



**Table 6.5** *Effect of exogenous variables on hyperventilation for the non-cardiac group*

| Variable | Direct effect | Indirect effect | Total |
|---|---|---|---|
| Age | -0.23 | 0.23 | 0.00 |
| Anxiety | 0.55 | 0.10 | 0.65 |
| Depression | -0.48 | 0.60 | 0.12 |
| Somatisation | 0.94 | 0.00 | 0.94 |

Figure 6.2 shows the constructed model and the respective path coefficients and squared multiple correlations for the cardiac group. The goodness-of-fit test yielded a $\chi^2$-square of 2.41 (**df**=5, $p$=0.79), a goodness-of-fit index of 0.98 and an adjusted goodness-of-fit index of 0.94. The standardized root mean

square residual was 0.03 and an expected cross-validation index of 0.49. These indicators also suggest a good fit of this constructed model. As can been seen from Figure 6.2, it is somatisation that is directly related to anxiety (0.74) and depression (0.59). Hyperventilation and age are, according to the constructed model, not related to any of the other variables. Adding these variables to the model would produce a significant and therefore incorrect model.

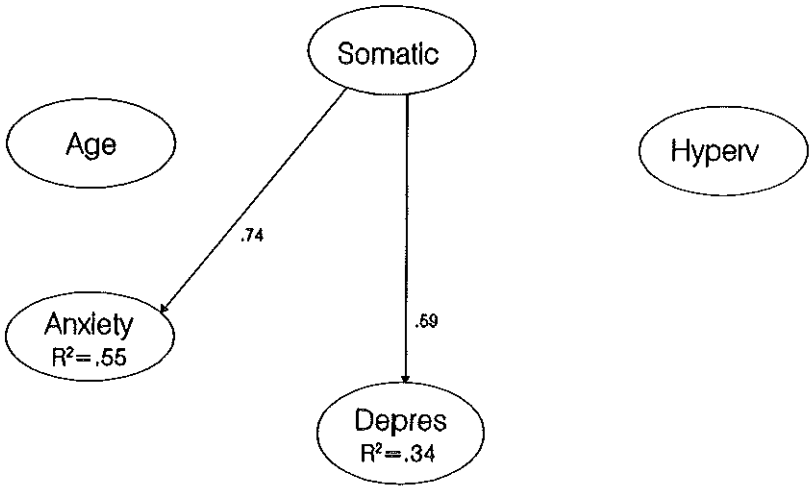
## 6.5 Discussion

In this study we found that, consistent with the recent literature on non-cardiac chest pain (6-10, 14-17), non-cardiac patients acquired significantly higher scores on the variables hyperventilation, anxiety, and somatisation than cardiac patients. We do of course realize that hyperventilation was only measured with a questionnaire. But as the study by Van Dixhoorn and Duivenvoorden (38) sowed a high sensitivity and specificity of the Nijmegen Questionnaire in relation to the clinical diagnosis, we thought it justifiable to use the questionnaire as a close approximation of that clinical diagnosis. The average depression of the non-cardiac group was higher than that of the cardiac group, but did not reach statistical significance.

As the non-cardiac patients scored higher on all the measured characteristics, we were especially interested in the association between these variables and by means of LISREL analysis we were able to model these associations quantatively. Our constructed model indicates that anxiety and somatisation have a large total positive effect on hyperventilation, implying that higher anxiety and/or somatisation levels increase hyperventilation. Anxiety also has a major effect on depression. Depression, in turn, has a direct negative effect on hyperventilation, but a positive indirect effect via somatisation, giving a total impact which is negligible. The total effect of age on hyperventilation is zero, as increased age reduces hyperventilation but on the other hand enhances it through augmenting somatisation.

For a more definite answer concerning the findings, the constructed models should be replicated. In such studies facilities should be created to maximalise the key concept by other methods, such as interviews, observations and clinical judgements. Assuming that the constructed models appear to be stable, then a number of implications for medical as well as psychological treatment of non-cardiac chest pain have to be considered.

**Figure 6.2** *Structural model of chest pain for the cardiac patients (N=47; $\chi^2$=2.41; goodness-of-fit index (GFI)= 0.98; adjusted goodness-of-fit index (AGFI)= 0.94)*




Medically, the cardiologist should, after eliminating the possibility of a cardiac cause for the chest pain, by means of standard diagnostic testing, refer the non-cardiac patient to a psychologist or psychiatrist more quickly and without hesitation. Psychologically, the treatment of the non-cardiac patient should be tailored, in that the present (effective) treatment methods (e.g. (44-47) focus primarily on the breathing problems associated with hyperventilation. In this study we have shown that it is mainly anxiety and somatisation which are at the basis of hyperventilation. We would therefore recommend that these two variables need closer attention when treating non-cardiac patients.

For the cardiac group it is ascertained that the proven somatic complaints, have, not surprisingly, an augmenting effect on anxiety and depression and not vice versa. Hyperventilation in this group is very low, and does not have any effect on, or indeed is itself not effected by, any of the other psychological variables. Here too, the results should have implications for the psychological aspects of medical treatment. The task of the treating cardiologist should be in the prevention and possibly early detection of feelings of anxiety and/or depression. This prevention could conceivably be accomplished by giving

adequate information concerning the proven coronary disease. Early detection of the development or existence of an anxiety reaction or a vital depression could be achieved by simply questioning the patients on the specific characteristics related to both disorders.

We believe that the empirical psychological modelling of chest pain with the LISREL technique is of great relevance. It provides a means to model quantatively the underlying mechanisms of the maladaptive phenomena of non-cardiac chest pain and possibly thereby to tailor specific treatment methods. As such vast numbers of chest pain patients appear to have non-cardiac chest pain and follow-up studies show that non-cardiac patients still suffer from chest pain long after they have been reassured that 'nothing is wrong' (15, 20, 21, 23, 48), more attention into the implementation of appropriate treatment of non-cardiac chest pain is crucial. With this study we hope to have set a further step in this direction.

## 6.6 References

1. Serlie AW, Erdman RAM, Passchier J, Trijsburg RW, Ten Cate FJ. Psychological aspects of non-cardiac chest pain. Psychother Psychosom 1995; 64:62-73.
2. Hartstone H. On heart disease in the army. Am J Med Sci 1864; 48: 89-92.
3. Stillé A. Address before the Philadelphia Country Medical Society. Philadelphia: Collins, Printer, 1863: 18-19.
4. Lewis T. The soldier's heart and the effort syndrome.New York: Paul B. Hoeber, 1919:1-103.
5. Levine SA. The origin of the term neurocirculatory asthenia. N Eng J Med 1965; 273:604-605.
6. Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med. 1984; 14(1): 51-61.
7. Channer KS, Papouchado M, James MA, Rees JR. Anxiety and depression in patients with chest pain referred for exercise testing. Lancet 1985; 2(8459): 820-823.
8. Beitman BD, Basha I, Flaker G, DeRosear L, Mukerji V, Lamberti JW. Major depression in cardiology chest pain patients without coronary artery disease and with panic disorder. J Affective Disord 1987; 13(1):51-59.

9. Katon W, Hall ML, Russo J, et al. Chest pain: relationship of psychiatric illness to coronary arteriographic results. Am J Med 1988; 84(1):1-9.
10. Cormier LE, Katon W, Russo J, Hollifield M, Hall ML, Vitaliano PP. Chest pain with negative cardiac diagnostic studies. Relationship to psychiatric illness. J Nerv Ment Dis 1988; 176(6):351-358.
11. Potts SG, Bass CM. Psychological morbidity in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. Psych Med 1995; 25(2):339-347.
12. Costa PT, Zonderman AB, Engel BT, Baile WF, Brimlow DL, Brinker J. The relation of chest pain symptoms to angiographic findings of coronary artery stenosis and neuroticism. Psychosom Med. 1985; 47(3):285-293.
13. Papanicolaou MN, Califf RM, Hlatky MA, et al. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. Am J Cardiol 1986; 58(13):1181-1187.
14. Bass C, Chambers JB, Kiff P, Cooper D, Gardner WN. Panic anxiety and hyperventilation in patients with chest pain: a controlled study. Q J Med 1988; 69(260):949-959.
15. Lantinga LJ, Sprafkin RP, McCroskery JH, Baker MT, Warner RA, Hill NE. One-year psychosocial follow-up of patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1988; 62(4): 209-213.
16. Herrmann C, Scholz KH, Kreuzer H. [Psychologic screening of patients of a cardiologic acute care clinic with the German version of the Hospital Anxiety and Depression Scale] Psychologisches Screening von Patienten einer kardiologischen Akutklinik mt einer deutchen Fassung der "Hospital Anxiety and Depression" (HAD)-Skala. Psychother Psychosom Med Psychol. 1991; 41(2):83-92.
17. Alexander PJ, Prabhu SG, Krishnamoorthy ES, Halkatti PC. Mental disorders in patients with noncardiac chest pain. Acta Psychiatr Scan 1994; 89(5): 291-293.
18. Mayou R, Bryant B, Forfar C, Clark D. Non-cardiac chest pain and benign palpitations in the cardiac clinic. Br Heart J 1994; 72:548-553.
19. Proudfit WL, Bruschke AVG, Sones FM Jr. Clinical course of patients with normal or slightly or moderately abnormal coronary arteriograms: 10-year follow-up of 521 patients. Circulation 1980; 62:712-717.
20. Pasternak RC, Thibault GE, Savoia M, DeSanctis RW, Hutter AM. Chest pain with angiographically insignificant coronary arterial obstruction. Clinical presentation and long-term follow-up. Am J Med 1980; 68: 813-817.
21. Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary arteriograms: a follow-up study of functional status. N Eng J Med 1980; 303(22):1249-52.

22. Wilcox RG, Roland JM, Hampton JR. Prognosis of patients with "chest pain ?cause". Br Med J 1981; 282:431-433.
23. Isner JM, Salem DN, Banas JS Jr., Levine HJ. Long-term clinical course of patients with normal coronary arteriography: Follow-up study of 121 patients with normal or nearly normal coronary arteriograms. Am Heart J 1981; 102:645-653.
24. Bass C, Wade C, Hand D, Jackson G. Patients with angina with normal and near normal coronary arteries: clinical and psychosocial state 12 months after angiography. Br Med J Clin Res Ed. 1983; 287(6404): 1505-1508.
25. Wielgosz AT, Fletcher RH, McCants CB, McKinnis RA, Haney TL, Williams RB. Unimproved chest pain in patients with minimal or no coronary disease: a behavioral phenomenon. Am Heart J 1984; 108(1): 67-72.
26. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. J Am Coll Cardiol 1986; 7(3):479-483.
27. Van Dorpe A, Piessens J, Willems JL, De Geest H. Unexplained chest pain with normal coronary arteriograms. A follow-up study. Cardiology. 1987; 74(6):436-443.
28. Serlie AW, Duivenvoorden HJ, Passchier J, Ten Cate FJ, Deckers JW, Erdman RAM. Empirical psychological modelling of chest pain; a comparative study. J Psychosom Res (in press).
29. Chambers JB, Kiff PJ, Gardner WN, Jackson G, Bass C. Value of measuring end tidal partial pressure of carbon dioxide as an adjunct to treadmill exercise testing. Br Med J (Clin Res Ed) 1988; 296(6632): 1281-1285.
30. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Effect of hyperventilation and mental stress on coronary blood flow in syndrome X. Br Heart J 1993; 69(6):516-524.
31. Mayou R. Invited review: Atypical chest pain. J Psychosom Res 1989; 33(4): 393-406.
32. Bass C, Gardner WN, Jackson G. Abnormal breathing patterns associated with angina-like chest pain. Br J Clin Pract. 1986; 40(1):25-27.
33. Beck JG, Berisford MA, Taegtmeyer H. The effects of voluntary hyperventilation on patients with chest pain without coronary artery disease. Behav Res Ther 1991; 29:611-621.
34. Moreyra AE, McGough WE, Hosler M, Kostis JB. Clinical improvement of patients with chest pain and normal coronary arteries after coronary arteriography: The possible role of hyperventilation syndrome. Int J Cardiol 1982; 2:306-308.
35. Bass C, Chambers JB, Gardner WN. Hyperventilation provocation in patients with chest pain and a negative treadmill exercise test. J Psychosom Res 1991; 35(1):83-89.

36. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. Br J Psychiatr 1976; 128: 280-289.
37. Evers A, Van Vliet-Mulder JC, Ter Laak J. [Documentation of tests and testreseach in the Netherlands] Documentatie van tests en testresearch in Nederland.Assen: Van Gorchum, 1992
38. Van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. J Psychosom Res. 1985; 29(2): 199-206.
39. Cohen J. Statistical power analysis for the behavioral sciences.Hillsdale: Erlbaum, 1988
40. Gardner MJ, Altman DG. Statistics with Confidence: confidence intervals and statistical guidelines.London: British Medical Journal, 1989
41. SPSS-Inc. Statistical package for the social sciences.Chicago: 1990
42. Cudeck R, Browne MW. Cross-validation of covariance structures. Multivar Beh Res 1983; 18:147-157.
43. Jöreskog K, Sörbom D. LISREL 8: Structural equation modeling with the simplis command language.Chicago: Scientific Software International, Inc., 1993
44. Fensterheim H, Wiegand B. Group treatment of the hyperventilation syndrome. Int J Group Psychoth 1991; 41(3):399-403.
45. Girotti LA, Crosatto JR, Messuti H, et al. The hyperventilation test as a method for developing successful therapy in Prinzmetal's angina. Am J Cardiol 1982; 49(4):834-841.
46. Garssen B, Rijken H. Clinical aspects and treatment of the Hyperventilation Syndrome. Beh Psychoth 1986; 14(1):46-68.
47. Hegel MT, Abel GG, Etscheidt M, Cohen-Cole S, Wilmer CI. Behavioral treatment of angina-like chest pain in patients with hyperventilation syndrome. J Behav Ther Exp Psychiatry 1989; 20(1):31-39.
48. Potts SG, Bass CM. Psychosocial outcome and use of medical resources in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. Q J Med 1993; 86(9):583-593.

# 7. General Discussion

## 7.1 Introduction

The psychological differences between non-cardiac and cardiac chest pain patients have been well documented in the contemporary literature (1-5). These studies have shown that non-cardiac patients have a higher level of psychological morbidity in the sense that they show higher levels of anxiety, depression, hyperventilation and panic disorder. The results of the studies combined in this thesis are in line with these previous findings.

In our first study (comparative: chapter 3) we studied 67 non-cardiac and 47 cardiac patients on average 1.3 years after their initial visit to their treating cardiologist. In this study we found, consistent with the literature, that non-cardiac patients were significantly more anxious than cardiac patients, as measured on the Hospital Anxiety Depression Scale (HAD) (6) and Symptom Check List (SCL-90) (7). Furthermore, the non-cardiac patients showed higher levels of somatisation, obsessive compulsive behaviour, psychoneuroticism and hyperventilation than the cardiac patients. Compared to the norm scores the non-cardiac patients also had high scores.

By means of a logistic regression analysis we were able to correctly discriminate 75.4% of the patients as being non-cardiac and cardiac respectively. This performance was reached with only the SCL-90 anxiety scale comprising 10 questions and the hyperventilation questionnaire comprising 16 questions.

In our second study (baseline: chapter 4) we studied 55 non-cardiac and 43 cardiac patients at their initial visit to the cardiology out-patient's clinic. The results of this study depict the essence of this thesis, as our main objective was to discover any (psychological) differences between non-cardiac and cardiac patients in the very early stages of diagnostic testing. We subsequently found that the cardiac patients suffered more from chest pain typical for angina and had more vigour than the non-cardiac patients. The non-cardiac patients revealed significantly higher levels of interpersonal sensitivity, displeasure, fears related to bodily injury, death and illness, depression, fatigue and mood disturbance (later three measured with the profile of mood states POMS) (8),

compared to the cardiac patients. By means of logistic regression analysis we were able to correctly discriminate 79.6% of the patients as being non-cardiac and cardiac respectively. The high performance was based on chest pain typical for angina, fear for one's own health, feelings of physical disability, fatigue and fears related to bodily injury, death and illness.

In our third study (follow-up: chapter 5) we studied 72 (73%) of the baseline patients, 39 non-cardiac and 33 cardiac patients on average 1.6 years after their initial visit to their treating cardiologist. In this follow-up study the cardiac patients still showed more chest pain typical for angina and higher levels of vigour. Similarly, the non-cardiac patients still revealed more fear for their own health and fears related to bodily injury, death and illness. Additionally, the non-cardiac patients had higher levels of HAD-anxiety and showed considerably less confidence in doctors than their cardiac counterparts. By means of logistic regression analysis we were able to correctly discriminate 75% of the patients as being non-cardiac and cardiac respectively. This performance was based on the variables fear for one's own health, tension and fears related to bodily injury, death and illness.

The addition made by our three studies is that we went one step further than contemporary studies by not only looking at the univariate differences, but also at all the variables jointly. For this purpose the data were analyzed using logistic regression analysis. As mentioned above, the models constructed with this multivariate technique were able to quite accurately predict non-cardiac chest pain. The high performance of the models ($\pm$ 80%) was achieved with a relatively small number of variables. In our baseline study, for instance, of the initial 333 questions, we found that only 51 questions were required to accurately (79.6%) detect non-cardiac chest pain in the early stages of cardiac testing (see appendix C for further details). Although the number of patients in all the studies were relatively small, we were able to test the stability of the models by using the method of crossvalidation. For all the model constructed we did indeed find that they were stable.

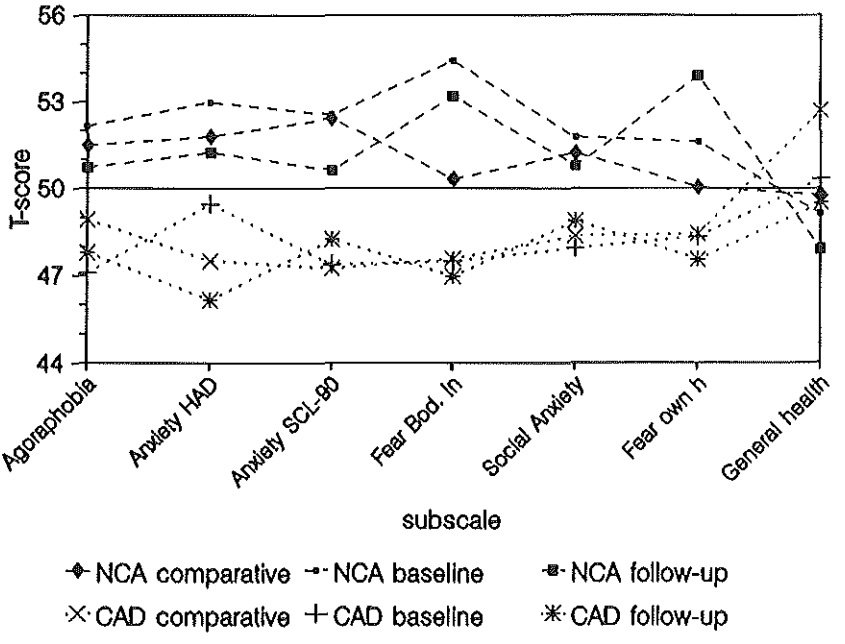
The concepts of the outcome measures of the model constructed with data from the comparative study (chapter 3), SCL-anxiety and hyperventilation, were so clear that we were able to study the causal relations of between hyperventilation, anxiety, depression and age, in more detail using the LISREL technique for model construction.

## 7.2 Comparison of the three studies

Transformation of the results of all three studies into T-scores, which have a mean of 50 and a standard deviation of 10, facilitates comparisons between the three studies. It should be noted that these T-scores are not adjusted for age and gender and accurate comparison between the comparative study (study 1) and the baseline study (study 2) and the follow-up study (study 3) is not possible.

The differences between the baseline study and the follow-up study, can formally be examined by means of regression analysis, whereby the follow-up measurement is used as the dependent variable and age, gender, cardiac diagnosis (NCA/CAD) and baseline measurement as the independent variables.

**Figure 7.1** *T-scores for anxiety measures for the comparative ($n_1$=114), baseline ($n_2$=72) and follow-up ($n_3$=72) study*




For this purpose the data of the patients participating in both studies were used.

### 7.2.1 Similarities

#### 7.2.1.1 Anxiety

Figure 7.1 shows the T-scores of the variables which measure various forms of anxiety. A clear discrepancy can be seen, for all three studies, between the non-cardiac and the cardiac patients, namely that the non-cardiac patients show higher levels of anxiety on most anxiety questionnaires.

#### 7.2.1.2 Depression

Figure 7.2 shows the T-scores of the variables which measure depression and factors related to depression such as displeasure, fatigue, tension and vigour (9). Although the discrepancy between the non-cardiac and the cardiac patients is not so clear as with anxiety, the non-cardiac patients, with the exception of vigour have higher levels of depression or depression related determinants. For vigour a lower level is less favourable.

#### 7.2.1.3 Somatogenic

As far as somatogenic determinants are concerned, depicted in Figure 7.3, the non-cardiac patients in all three studies show higher levels of somatisation and hyperventilation. For feelings of physical disability there is, however, no clear discrepancy.

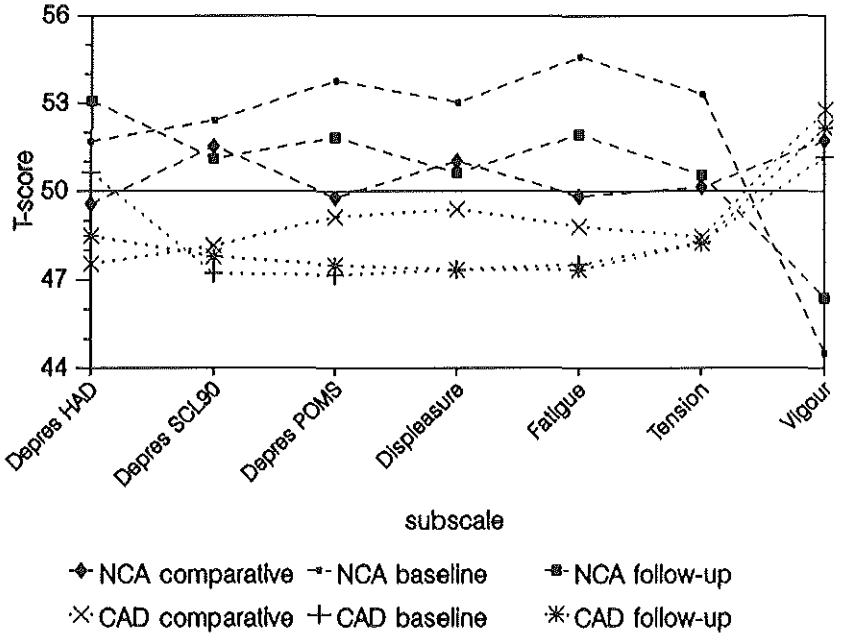
It is noteworthy to mention that the significant difference between the non-cardiac and the cardiac patients for hyperventilation in the comparative study is mainly due to a very low level for the cardiac patients. As can be seen for the non-cardiac patients, the level of hyperventilation is the same in both the comparative and the baseline study. The low hyperventilation level of the cardiac patients in the comparative study may be due to the significant differences between the two patient categories, found in smoking behaviour. It is conceivable that smoking reduces hyperventilation, as it has a sedative properties and increases $CO_2$ levels. Additionally, there were significantly more men in the cardiac group in that comparative study. A study by Moreyra (10) into hyperventilation and chest pain has shown that men suffer less from hyperventilation.

### 7.2.2 Differences

#### 7.2.2.1 Anxiety

As can be seen from the T-transformations of the various anxiety measures (Figure 7.1) the levels of anxiety of the non-cardiac patients in the baseline study and the follow-up study are higher than the measures of the non-cardiac patients in the comparative study. This is most likely due to differences in patient population, such as a significant gender ratio; in the comparative study there were significantly more women in the non-cardiac group and it is well known (e.g. (11) that women show higher levels of anxiety. In the baseline study and in the follow-up study there were no significant gender differences.

**Figure 7.2** *T-scores for depression and depression related variables for the comparative ($n_1$=114), baseline ($n_2$=72) and follow-up ($n_3$=72) study*

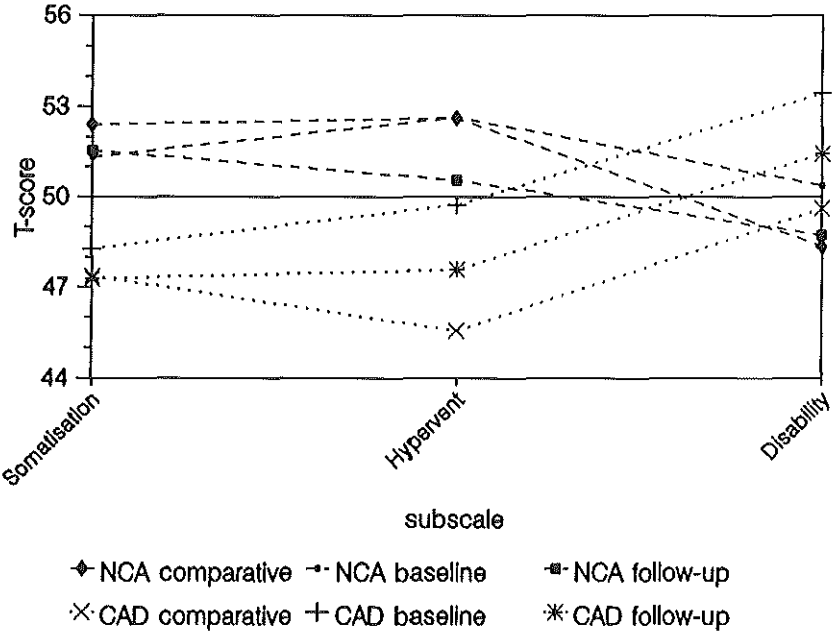



The increased fear for one's own health at follow-up, was only significant for the non-cardiac patients, as is implied by a significant diagnosis (NCA/CAD) in the regression equation, when comparing scores in baseline study to the follow-up study. This finding is not surprising since the pain in the non-cardiac

group is genuine. A cardiac cause has been ruled out and the non-cardiac patients conceivably worry about other, perhaps more serious, causes for their chest pain.

The reduction in agoraphobia ($p < 0.05$), and SCL-anxiety ($p < 0.05$) at follow-up was significant for both the non-cardiac and the cardiac patients, as is implied by a significant constant in the regression equation.

**Figure 7.3** *T-scores for the somatogenic variables for the comparative ($n_1$=114), baseline ($n_2$=72) and follow-up ($n_3$=72) study*




### 7.2.2.2 Depression

As far as depression and depression related variables are concerned (Figure 7.2), similar regression analysis as for anxiety show that the lower SCL-depression at follow-up is significant for both groups, as can been implied from a significant constant ($p < 0.05$) in the regression equation.

Vigour appears to be lower in the patient groups of the baseline study and the follow-up study compared to the patients of the comparative study. This too, is most likely due to the differences in study population, such as significantly more women in the non-cardiac group in the comparative study. For that

matter, the discrepancy between non-cardiac and cardiac patients on depression and depression related variables appears to be lower in the comparative study on all measured variables.

#### 7.2.2.3 Somatogenic

None of the changes between study 2 and study 3 of the somatogenic variables somatisation, hyperventilation and feelings of disability (Figure 7.3) are statistically significant.

#### 7.2.2.4 Other variables

For a large number of other variables the levels, for both non-cardiac and cardiac patients, are lower at follow-up. Psychopathology is significantly lower for both groups at follow-up than at baseline measurement. This is implied by the significant constant in the regression equation ($p < 0.05$). The same is true for interpersonal sensitivity ($p < 0.05$), psychoneuroticism ($p < 0.05$) and medical information seeking behaviour ($p < 0.01$). Most likely the general psychological 'problems' decrease over time and conceivably shift from general to more specific problems (e.g. anxiety, fears related to bodily injury, death and illness).

Obsessive compulsive behaviour significantly increases over time for both patient categories ($p < 0.01$). The uncertainty over the diagnosis in the non-cardiac groups may conceivably lead to an increase in the need to gain control over things and consequently lead to more obsessive compulsive behaviour. For the cardiac patient the knowledge of having a cardiac problem may possibly lead to a more intensive clamping on to familiar rituals.

Confidence in doctors decreases only significantly for the non-cardiac patients, as is implied by the diagnosis (NCA/CAD) being significant in the regression equation ($p < 0.01$). The decrease in confidence of doctors in the non-cardiac group in not surprising. Doctors can, after all, not find a (cardiac) cause for their chest pain complaints. Subsequently the non-cardiac patients are told that 'nothing is wrong', no further appointments are made and patients are left in a void.

### 7.3 Possible explanations and clinical relevance

The quantitative models constructed in our studies explicitly show that anxiety is a major factor related to non-cardiac chest pain. In our LISREL analysis (chapter 6) we were even able to demonstrate that hyperventilation, which is manifest in many non-cardiac patients (e.g.(10, 12-18), is positively effected by anxiety and somatisation, implying that, for non-cardiac patients, higher anxiety and/or somatisation levels increase hyperventilation.

Despite not having studied the specific reasons for the elevated anxiety in the non-cardiac in any of our studies, we will, however, mention some plausible theories.

From a psychodynamic point of view the basis of handling conflicts and associated emotions is laid in childhood. Especially the anxiety emotion is crucial. Conflicts can give raise to so much anxiety, that other feelings which are easier to bear, are experienced instead of the original emotion. In that way pain can form a protection against unbearable emotions, becoming conscious (see e.g. (19).

Likewise, in the psychodynamic point of view, the development from a dependent baby to an independent adult can play a major part in the association between anxiety and non-cardiac chest. Problems with parent-separation can lead to intrapsychic conflicts accompanied by feelings of hostility against parents and possible feelings of guilt. Successful individuation is only achieved when certain bothering conscience feelings can be set aside. If one is not successful in achieving this, feelings of guilt will prevail, possibly leading to a desire for self-punishment (e.g. by thoughts about death caused by cardiac problems). Results from Eifert's study (20), for that matter, show that 80% of his non-cardiac patients had experienced some form of separation from a significant person before their first episode of chest pain. Likewise Gittelman and Klein (21) related childhood separation experiences to adult anxiety disorders and Lynch (22) reported that interruptions of interpersonal contact have a powerful effect on the cardiovascular system.

Beunderman and Duyvis (23) propose an affective-cognitive view as an important factor contributing to anxiety and perceived chest pain. They emphasize that the relation between physical complaints and fear of cardiac problems

is established and maintained by processes such as 1) *labelling*, by which the patient attributes any pain in the chest region to an approaching heart attack. This label in turn is then a source of fear, as it can provoke a physical reaction. 2) *Anticipating*, even when the patient does not have any complaints, complaints may be anticipated, which can itself provoke feelings of anxiety. Any feelings induced by this anticipation could be labelled as cardiac complaints. 3) *Attention*, labelling and anticipation may increasingly direct the patient's attention towards specific parts of the body. As a result the level of perception is decreased, and all kinds of sensations become perceptible. These sensations are then labelled as cardiac complaints.

Consequently, non-cardiac chest pain might best be seen as, if not caused then at least maintained by, a vicious circle. Higher levels of anxiety and depression lower pain perception thresholds (24). Perceived pain gives reason for feelings of anxiety and depression and the circle is complete.

Hyperventilation may be at the basis of initialising chest pain. It is for that matter strongly associated with non-cardiac chest pain (e.g. (10, 18) and in our first study (chapter 3) we also found a higher level of hyperventilation in the non-cardiac group. A subsequent LISREL analysis on the data demonstrated a strong relation between anxiety and hyperventilation. In a detailed analysis by Eifert (20) on a subgroup of non-cardiac chest pain patients (cardiophobics), he suggested that the mechanisms initiating panic disorder may be similar to those initiating cardiophobia. Ley (25), for instance, reported that the onset of panic attacks consisted of an interaction between hyperventilation and fear, with symptoms of hypocapnia preceding the fear. Wolpe and Rowan (26) stated that the initial panic attack is an unconditioned response to a disturbing set of somatic changes, probably invoked by hyperventilation, in a person that is likely to be habitually anxious and hypersensitive. Any number of somatic or external stimuli coinciding with the first panic are capable of triggering subsequent attacks on a conditioned basis. These stimuli include early physiological effects of hyperventilation, fearful thoughts and a variety of situational stimuli.

With cardiophobia, a similar course of events is possible. The initial attack is probably an uncued false alarm to a disturbing set of bodily changes most likely to be the result of hyperventilation and chest muscle tension. This in turn will probably increase heart rate and/or invoke chest pain. The cardiophobic will, contrary to the person who develops panic disorder, focus on changes in the

chest pain area and interpret them in a catastrophic way as signs of an impending heart attack or other heart problem (20).

A person may learn to associate increases in chest pain with all kinds of stimuli and situations that preceded previous chest pain attacks. Consequently, thoughts about these stimuli or situations may trigger anticipatory anxiety and associated physiological changes.

Salkovskis (27) proposes a theoretical framework which concurs with the idea of a vicious circle. Additionally, he emphasises different ways to break through the vicious circle, by using verbal techniques and behavioural experiments, such as hyperventilation provocation tests, to 'decatastrophize' the explanations of anxiety components. Positive treatment results were also accomplished using cognitive-behavioural oriented psychotherapy (28, 29) (see also chapter 2).

It is so important to realize that many non-cardiac patients continue to experience chest pain, even after they had been reassured and told that there was nothing wrong with their heart. Ockene's study (30), for that matter, noted that 70% of the non-cardiac patients still complained of chest pain after an average follow-up period of 16 months. Likewise, in our own follow-up study (chapter 5) 35% of the non-cardiac patients perceived their chest pain as the same or worse than at baseline.

Taking the continuing suffering and treatability of non-cardiac chest pain into account it seems highly relevant to recognize and treat non-cardiac chest pain in the early stages of diagnostic testing. The model constructed in our cross-sectional study (chapter 4) seems most appropiate for that purpose, as the questionnaires were completed at the first visit to the cardiologist. It should be clear, however, that the constructed model can by no means replace diagnostic testing, but should be considered a helpful instrument, for doctors as well as patients, to recognize cardiophobia and treat it accordingly. In our view, all standard medical diagnostic testing should be done first to exclude coronary artery disease. Only if the cardiologic tests show no somatic cause, the 51 questions, represented by 5 constructs, significantly contributing to the model should be utilized as to see whether psychological problems may be at the basis of the problem. Our follow-up study, for that matter, showed that that the psychological problems of the non-cardiac patients remain over time and that a more adequate treatment for this group should be considered.

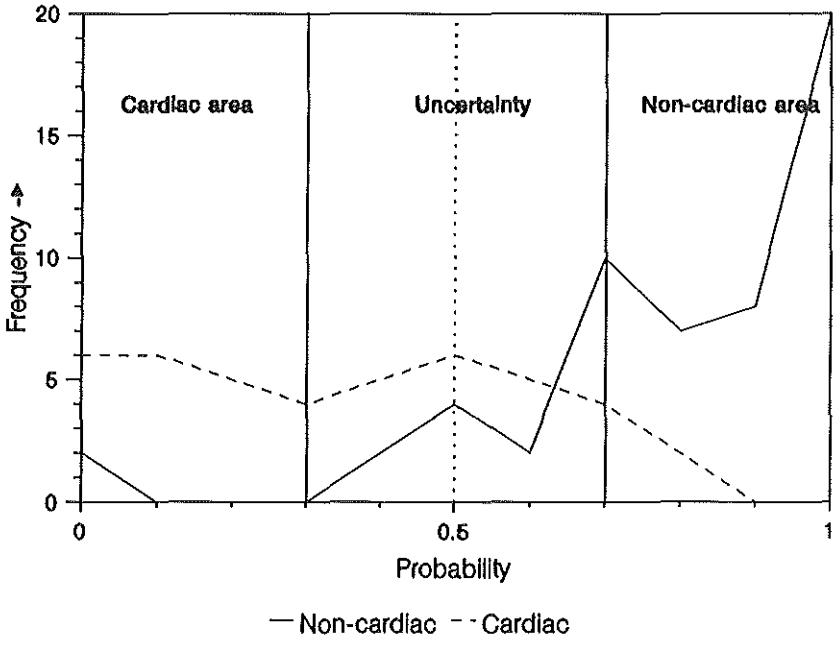
## 7.4 Methodology

In this paragraph we will discuss some implications of the methodology used in the studies combined in this thesis.

### 7.4.1 Cut-off point

The constructed quantitative models of our three studies have a performance of approximately 80%, which indicates that 20% of the patients were incorrectly classified. This is partly due to the overlap caused by the cutt-off point of the logistic regression model. Although non-cardiac patients generally show higher levels of anxiety, depression, hypochondria and hyperventilation, there are of course also individual cardiac patients who are anxious, depressed, hypochondriac or who hyperventilate.

**Figure 7.4** *Plot of the probability of being non-cardiac set against frequency of being classified as cardiac or non-cardiac*




Similarly, this variance applies to individual non-cardiac patients, in that some non-cardiac patients may have lower than average levels of anxiety, depression, hypochondria or hyperventilation.

Logistic regression analysis places the cut-off point for the differentiation of cardiac/non-cardiac at p=0.50. This means that if an individual patient has a probability between 0.0 and 0.5 of being non-cardiac he or she will be categorised as cardiac. A patient with a probability of being non-cardiac between 0.5 and 1.0 will be categorised as non-cardiac. Consequently there will be a considerable overlap of the raw data for both patient categories (see Figure 7.4). In this respect, a higher performance of the model might be achieved by specifying different cut-off points and defining three prediction categories; 1) cardiac (e.g. 0-30%), 2) uncertainty about diagnosis (e.g. 30-70%) and 3) non-cardiac (e.g. 70-100%).

### 7.4.2 Omitted variables

Before our investigation into non-cardiac chest pain was commenced a review was conducted of the relevant literature (chapter 2). Most of these studies had focused on anxiety, depression (e.g. (1, 2), hyperventilation (e.g. (31), simple phobias and panic disorder (e.g. (4, 5, 32). Except for panic disorder, as it is a psychiatric diagnosis and cannot be measured with a questionnaire, all these variables were also measured in our studies. Conceivably, we omitted several differentiating variables, such as social and physical activity and relational and work problems. Perhaps more attention should also have been given to specific characteristics of cardiac patients, such as type-A behaviour (33) or perceived stress.

### 7.4.3 Methodological limitations

In the studies combined in this thesis we set out to construct a quantitative model which could differentiate between patients with cardiac and non-cardiac chest pain. We wanted to achieve this with as little extra strain to patients as possible and on the basis of the profiles of patients visiting the cardiology outpatient's clinic for the first time. For that reason we only used questionnaires and the gathering of data was not to interfer with normal diagnostic procedure; patients did not undergo extra or fewer diagnostic tests because of our study and the study was also not limited to a selected number of cardiologists. It is therefore conceivable that patients were not as accurately classified as cardiac or non-cardiac as might be after a fixed series of well described cardiological tests and related criteria. Futhermore a patient might be classified as non-

cardiac but later appeared to have some other somatic disease afterall. On the other hand, a patient classified as cardiac might have something cardiacally wrong but this may not cause the chest pain. This way of classification can of course have implications for the accuracy of the constructed model. The limitations, furthermore, imply that the studies were not standardised and the results can therefore not be generalized to all chest pain patients, especially as we left out chest pain patients, whose complaints had an other somatic cause.

Additionally, the studies were only conducted at the Rotterdam University Hospital. Consequentially, a selection bias is conceivable. General practitioners might be inclined to refer patients with more complicated medical problems to a University Hospital. Furthermore, social economic status and level of education may possibly also differ from patients refered to a non-academic hospital.

In the models we constructed, we adjusted for age and gender, so that the model would be applicable regardless of age and gender. It is well known that the prevalence of coronary artery disease, and therefore the absence of it, is strongly related to age and gender. In our cross-sectional study (chapter 4) we did, however find that a model with only age and gender can correctly classify 77% of the patients as being cardiac or non-cardiac, whereas a model also including psychological variables can correctly classify 87% of the patients. Crossvalidation within the sample, as described in chapter 4, proved that our model was stable.

As a consequence of the limitations mentioned above, the models constructed in our studies should be seen as a good starting point for future research.

### 7.5 Future research

To obtain a valid instrument for the early detection of non-cardiac chest pain our explorative quantitative model should be tested in a standardised setting. Ideally, all patients should undergo the same standardised diagnostic testing and the results of the test should be viewed by a number of cardiologist, who have been trained to achieve a high interrater-reliability. A closer look at all possible other somatic causes should be made as to be sure that the complaints of the patients in the non-cardiac group are indeed non-cardiac and non-somatic. Furthermore, a close look should be made at the need for psychological help in both patient groups.

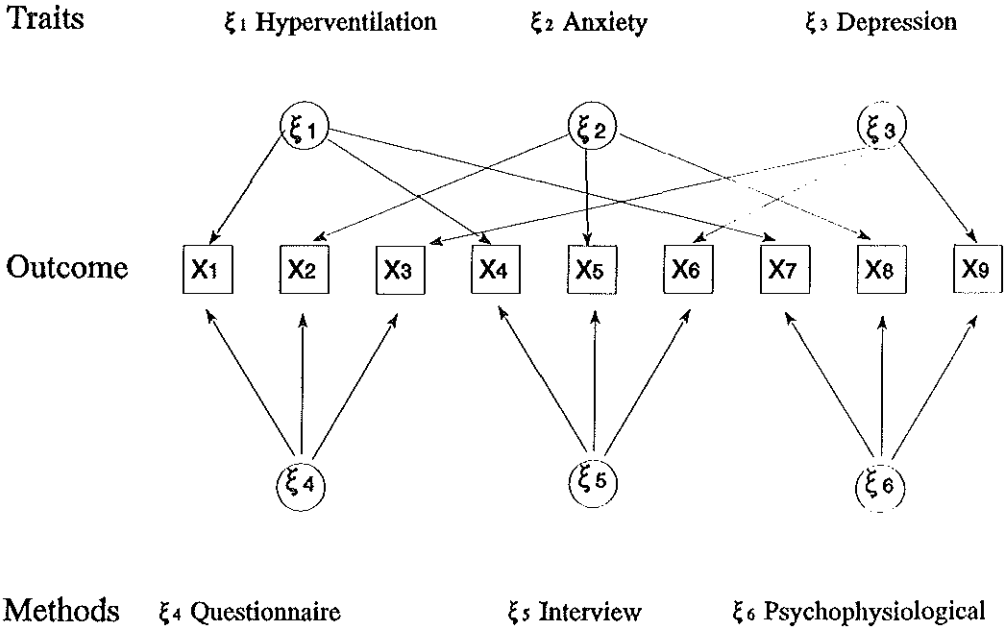
It is also important to study the psychological problems, such as anxiety and hypochondria, in a standardised clinical manner, for instance using DSM-III-R (9). It would be interesting to study the psychological aspects of both CAD patients and NCA patients after medical respectively psychological treatment. Additionally, the study should be set up as a multi-centre trial encompassing more patients, also including non-academic hospitals, as to be able to correct the model for differences in for instance, severity of the complaints, social economic status or level of education. While it was not our purpose to investigate the psychological variables as a cause of chest pain, the following recommandations can be made for studies which want to investigate this hypothesis. Such research might focus on the underlying characteristics associated with the apparent higher levels of anxiety in the non-cardiac group, such as (childhood) separation experiences (20). It would also be of great interest to conduct a detailed study into the psychophysiological aspects of non-cardiac chest pain. In this respect both a closer look at hyperventilation and an investigation of the physiological changes generated by the hypothesised anticipation (23) might reveal interesting mechanisms.

A multimethod-multitrait approach might be appropriate for a more detailed understanding of non-cardiac chest pain. With this method various constructs are measured in various methods. Hyperventilation, anxiety and depression, for instance, could be measured with a questionnaire, by means of an interview and psychophysiologically. The results of the three measurement methods can subsequently be compared (see Figure 7.5). Advantages of such an approach lie in the possibilities of correcting for the bias of the measurement method and recognition of masking which might occur with questionnaires.

LISREL-analysis would appear to be the most suitable technique for studying the relevant importance between the various constructs at the basis of non-cardiac chest pain.

Of utmost importance for the patients diagnosed as being non-cardiac is an adequate and tailored treatment of the disorder. Making use of the relevant literature (e.g. (27, 28) it would be appealing to set up a clinical trial comprising different treatment methods.

**Figure 7.5** *A Multimethod-Multitrait model*

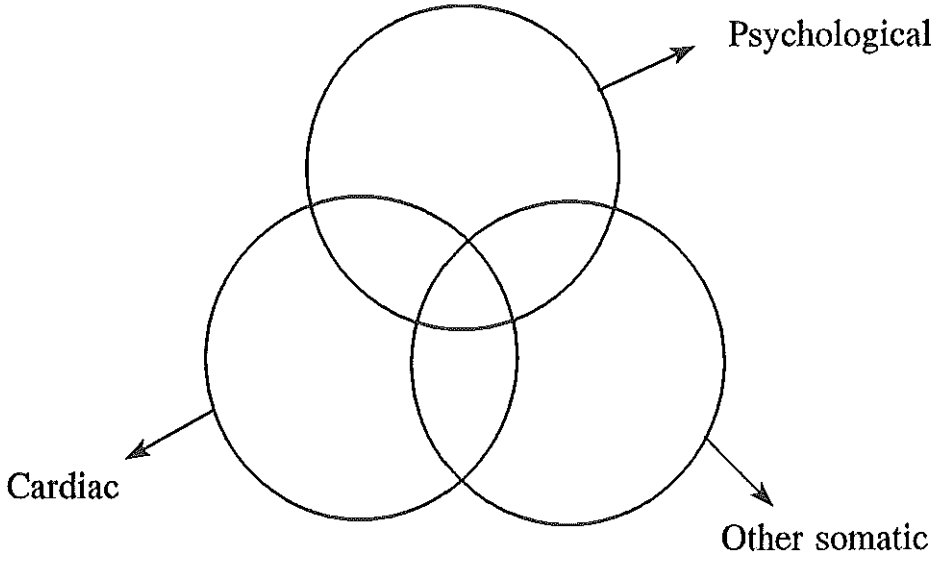



## 7.6 Recommendations for clinical practice

As can be seen from Figure 7.6, chest pain can have various, or even multiple causes. It should be clear that the models constructed in our studies should by no means replace diagnostic testing, but should be considered helpful instruments, for doctors as well as patients, to assess patients with non-cardiac chest pain more objectively. In our view, standard medical diagnostic testing should be conducted first to exclude coronary artery disease. Only if the cardiologic tests are inconclusive, the results of the subscales (appendix C) significantly contributing to the differentiation between non-cardiac and cardiac patients should be utilized. In this way one can trace the group of patients who show psychological morbidity such as anxiety and hypochondria and who have a tendency to hyperventilate; all non-cardiac qualifications. Once these non-cardiac patients have been identified and other somatic causes ruled out, their physicians should contemplate referring them for psychological treatment. Referral for psychological treatment is often thought to encounter resistance by

the patient (36), but a recent study (37), for that matter, has shown that most patients with unexplained physical symptoms, who might benefit from additional psychological treatment are willing to accept it, whereas those who rejected psychological treatment were those with the least serious problems.

**Figure 7.6** *Venn diagram of the possible causes of chest pain. (The size of the circles and the degree of overlap do not indicate the relative prevalence of the causes)*




Implementation of this policy will most likely be beneficial for non-cardiac patients as their complaints will be recognised and treated, but also for hospitals and doctors as it reduces workload and costs.

## 7.7 References

1. Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med. 1984; 14(1): 51-61.

2. Channer KS, Papouchado M, James MA, Rees JR. Anxiety and depression in patients with chest pain referred for exercise testing. Lancet 1985; 2(8459): 820-823.
3. Beitman BD, Basha I, Flaker G, DeRosear L, Mukerji V, Lamberti JW. Major depression in cardiology chest pain patients without coronary artery disease and with panic disorder. J Affective Disord 1987; 13(1): 51-59.
4. Katon W, Hall ML, Russo J, et al. Chest pain: relationship of psychiatric illness to coronary arteriographic results. Am J Med 1988; 84(1): 1-9.
5. Cormier LE, Katon W, Russo J, Hollifield M, Hall ML, Vitaliano PP. Chest pain with negative cardiac diagnostic studies. Relationship to psychiatric illness. J Nerv Ment Dis 1988; 176(6): 351-358.
6. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67(6): 361-370.
7. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. Br J Psychiatr 1976; 128: 280-289.
8. Wald FDM, Mellenbergh GJ. [The shortened version of the Dutch translation of the Profile of Mood States] De verkorte versie van de Nederlandse vertaling van de Profile of Mood States. Ned Tijdschr Psychol 1990; 45: 86-90.
9. APA. Diagnostic and statistical manual of mental disorders, 3rd ed. Revised. Washington DC: APA, 1987. .
10. Moreyra AE, McGough WE, Hosler M, Kostis JB. Clinical improvement of patients with chest pain and normal coronary arteries after coronary arteriography: The possible role of hyperventilation syndrome. Int J Cardiol 1982; 2: 306-308.
11. Schocken DD, Greene AF, Worden TJ, Harrison EE, Spielberger CD. Effects of age and gender on the relationship between anxiety and coronary artery disease. Psychosom Med 1987; 49(2): 118-26.
12. Chambers JB, Kiff PJ, Gardner WN, Jackson G, Bass C. Value of measuring end tidal partial pressure of carbon dioxide as an adjunct to treadmill exercise testing. Br Med J (Clin Res Ed) 1988; 296(6632): 1281-1285.
13. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Effect of hyperventilation and mental stress on coronary blood flow in syndrome X. Br Heart J 1993; 69(6): 516-524.
14. Mayou R. Invited review: Atypical chest pain. J Psychosom Res 1989; 33(4): 393-406.
15. Bass C, Gardner WN, Jackson G. Abnormal breathing patterns associated with angina-like chest pain. Br J Clin Pract. 1986; 40(1): 25-27.
16. Beck JG, Berisford MA, Taegtmeyer H. The effects of voluntary hyperventilation on patients with chest pain without coronary artery disease. Behav Res Ther 1991; 29: 611-621.

17. Bass C, Chambers JB, Gardner WN. Hyperventilation provocation in patients with chest pain and a negative treadmill exercise test. J Psychosom Res 1991; 35(1): 83-89.
18. Bass C, Chambers JB, Kiff P, Cooper D, Gardner WN. Panic anxiety and hyperventilation in patients with chest pain: a controlled study. Q J Med 1988; 69(260): 949-959.
19. Pilowsky I. Psychodynamic aspects of the pain experience. In: Sternbach RA, ed. The psychology of pain. New York: Raven Press, 1978: 203-217.
20. Eifert GH. Cardiophobia: a paradigmatic behavioural model of heart-focused anxiety and non-anginal chest pain. Behav Res Ther 1992; 30(4): 329-345.
21. Gittelman R, Klein DF. Relationship between separation anxiety and panic and agoraphobic disorders. Symposium of the World Psychiatric Association, Section Clinical Psychopathology: Physiological basis of anxiety (1983, Vienna, Austria). 1984; 17(Suppl 1): 56-65.
22. Lynch. The language of the heart: the body's response to human dialogue. New York: Basic Books, 1985.
23. Beunderman R, Duyvis BJ. Cardiac Phobia. In: Kaptein AA, Ploeg HMvd, Garssens B, Scheurs PJG, Beunderman R, ed. Behavioural Medicine. Chichester: John Wiley & Sons, 1990: 95-107.
24. Bradley LA, Richter JE, Scarinci IC, Haile JM, Schan CA. Psychosocial and psychophysical assessments of patients with unexplained chest pain. Am J Med 1992; 92(5A): 65S-73S.
25. Ley R. Dyspneic-fear and catastrophic cognitions in hyperventilation panic attacks. Behav Res Ther 1989; 27: 549-554.
26. Wolpe J, Rowan VC. Panic disorder: a product of classical conditioning. Behav Res Ther 1988; 26: 441-450.
27. Salkovskis PM. Psychological treatment of noncardiac chest pain: the cognitive approach. Am J Med. 1992; 92(5A): 114.
28. Klimes I, Mayou RA, Pearce MJ, Coles L, Fagg JR. Psychological treatment for atypical non-cardiac chest pain: A controlled evaluation. Psychol Med 1990; 20(3): 605-611.
29. Nutzinger DO, Cayiroglu S, Grünberger J, Kieffer W, Zapotczky HG. Prognosis of cardiac phobia. Psychopathology 1990; 23: 63-72.
30. Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary arteriograms: A follow-up study of functional status. N Eng J Med 1980; 303: 1249-1252.
31. Beck JG, Berisford MA, Taegtmeyer H. The effects of voluntary hyperventilation on patients with chest pain without coronary artery disease. 1991; 29(6): 611-621.

32. Beitman BD, Basha I, Flaker G, et al. Atypical or nonanginal chest pain. Panic disorder or coronary artery disease? Arch Intern Med 1987; 147(9): 1548-1552.
33. Cooper T, Detre T, Weiss SM. Coronary prone behavior and coronary heart disease: a critical review. Ciculation 1981; 63: 1199-1215.
34. Evers A, Van Vliet-Mulder JC, Ter Laak J. [Documentation of tests and testreseach in the Netherlands] Documentatie van tests en testresearch in Nederland. Assen: Van Gorchum, 1992.
35. Van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. J Psychosom Res. 1985; 29(2): 199-206.
36. Shaw J, Creed F. The cost of somatization. J Psychosom Res 1991; 35(2-3): 307-312.
37. Speckens AEM, Van Hemert AM, Bolk JH, Hawton KE, Rooijmans HGM. The acceptability of psychological treatment in patients with medically unexplained physical symptoms. J Psychosom Res 1995; 39(7): 855-863.

# 8. Summary

Recent literatures has shown that of all patients referred to a cardiology out-patient's clinic because of chest pain, approximately 30% appear to have no detectable somatic grounds for their complaints. The objective of our research was to study the psychological and demographical characteristics of these non-cardiac patients and try do discover any differences between them and patients with a verifiable cardiac cause for their chest pain complaints. Once having established these differences our aim was to construct a diagnostic instrument in the form of a quantitative model. With this instrument the differentiation between cardiac and non-cardiac chest pain could be recognised more easily and in an earlier stage of diagnostic testing.

Chapter 1 is a general introduction to the concept of non-cardiac chest pain and some reasons for the necessity of researching the disorder are given.

Chapter 2 is a review of the contemporary literature concerning non-cardiac chest pain. Some possible explanations for the relationship between the complaints and the characteristics of non-cardiac patients are also presented. Furthermore, the ability of predicting non-cardiac chest pain from psychological factors and a range of follow-up studies is discussed. Finally the possibilities of treating cardiac phobia are mentioned.

In our first empirical study (chapter 3) we studied 67 non-cardiac and 47 cardiac patients on average 1.3 years after their initial visit to their treating cardiologist and found that non-cardiac patients were significantly more anxious than cardiac patients. Additionally, the non-cardiac patients showed higher levels of somatisation, obsessive compulsive behaviour, psychoneuroticism and hyperventilation. Logistic regression analysis on all the variables jointly showed that with the level of anxiety and hyperventilation was sufficient to correctly classify 75.4% of the patients as being non-cardiac or cardiac.

In our second study (chapter 4) we studied 55 non-cardiac and 43 cardiac patients at their initial visit to the cardiology out-patient's clinic and found that the non-cardiac patients had less chest pain typical for angina and less vigour. Additionally, the non-cardiac patients had significantly higher levels of interpersonal sensitivity, displeasure, fears related to bodily injury, death and illness, depression, fatigue and total mood disturbance. Logistic regression analysis on all the variables jointly showed that with the type of chest pain and the levels of fear for one's own health, feelings of physical disability, fatigue and fears related to bodily injury, death and illness were sufficient to correctly classify 79.6% of the patients as being non-cardiac or cardiac.

In our third study (chapter 5) we studied 72 (73%) of the previously mentioned baseline patients, 39 non-cardiac and 33 cardiac patients on average 1.6

years after their initial visit to their treating cardiologist. In this follow-up study 35% of the non-cardiac patients perceived their chest pain to be the same or even worse than at baseline. Additionally they showed less vigour and more fear for their own health and fears related to bodily injury, death and illness, higher levels of HAD-anxiety and considerably less confidence in doctors than their cardiac counterparts. Logistic regression analysis on all the variables jointly showed that the level of fear for one's own health, tension and fears related to bodily injury, death and illness were sufficient to correctly classify 75% of the patients as being non-cardiac or cardiac.

In chapter 6 a closer look is taken at the psychological factors underlying non-cardiac chest pain, using the data of our first empirical study. By means of the structural equation modelling technique LISREL the relations between the main discriminating variables for non-cardiac chest pain, hyperventilation, anxiety, depression, somatisation and age were studied for both the non-cardiac as well as the cardiac patients.

In chapter 7 the similarities and the differences between the three empirical studies are discussed.

The main conclusions from our three empirical studies are that one can fairly accurately differentiate non-cardiac from cardiac patients on the basis of the patient's psychological characteristics. Consistent with most follow-up studies mentioned in the literature, our follow-up study shows that psychological morbidity remains high after the non-cardiac patient has been reassured that 'nothing is wrong'. We would therefore like to advocate a policy of quicker referral, using the questionnaire developed in this thesis, to a trained psychologist or psychiatrist, especially as therapy has shown to be beneficial.

The use of the questionnaire developed in the studies of this thesis, will have to prove itself in a large study.

Uit de recente literatuur blijkt dat 30% van alle patiënten die verwezen worden naar een polikliniek cardiologie, vanwege pijn op de borst, geen aantoonbaar somatisch substraat voor de gepresenteerde pijnklachten heeft. Het doel van ons onderzoek was het bestuderen van de psychologische en demografische kenmerken van deze niet-cardiale patiënten. Tevens werd getracht de verschillen tussen voornoemde groep en patiënten met een aantoonbare cardiale oorzaak te vinden. Na deze verschillen vast te hebben gesteld, was ons doel een diagnostisch instrument te construeren in de vorm van een kwantitatief model. Met dit diagnosticum (zie appendix C) zijn de verschillen tussen cardiale en niet-cardiale patiënten gemakkelijker en in een eerder stadium van diagnostisch testen op te sporen.

Hoofdstuk 1 geeft een algemene introductie over niet-cardiale pijn op de borst en hierin worden enkele redenen gepresenteerd om deze stoornis nader te onderzoeken.

Hoofdstuk 2 presenteert een overzicht van de hedendaagse literatuur met betrekking tot niet-cardiale pijn op de borst. Hierbij worden enkele verklaringen gegeven voor de gepresenteerde klachten bij niet-cardiale patiënten. Bovendien wordt de mogelijkheid niet-cardiale pijn op de borst te voorspellen besproken en worden enkele vervolg studies gepresenteerd. Tenslotte worden verschillende behandelingsstrategieën besproken.

In onze eerste empirische studie (hoofdstuk 3) werden 67 niet-cardiale en 47 cardiale patiënten, gemiddeld 1,3 jaar na hun eerste bezoek aan hun behandelend cardioloog bestudeerd. Hierbij werd gevonden dat de niet-cardiale patiënten significant angstiger waren dan de cardiale patiënten. Bovendien bleken de niet-cardiale patiënten meer somatisatie, dwangmatig gedrag, psychoneuroticisme en hyperventilatie te vertonen. Logistische regressie analyse op alle variabelen toonde aan, dat de variabelen angst en hyperventilatie voldoende waren om 75,4% van de patiënten correct als niet-cardiaal danwel cardiaal te classificeren.

In onze tweede studie (hoofdstuk 4) onderzochten we 55 niet-cardiale en 43 cardiale patiënten bij hun eerste bezoek aan de polikliniek cardiologie. Conclusies waren dat de niet-cardiale patiënten minder vaak typisch angineuze pijn op de borst hadden en minder vitaliteit toonden. Bovendien hadden de niet-cardiale patiënten significant hogere scores op interpersoonlijke sensitiviteit, ontstemming, angst voor eigen gezondheid, depressiviteit, vermoeidheid en vrees voor lichamelijk letsel, dood en ziekte. Logistische regressie analyse op alle variabelen liet zien dat de variabelen type pijn op de borst, angst voor eigen gezondheid, invaliditeit, vermoeidheid en vrees voor lichamelijk letsel, dood en ziekte voldoende waren om 79,6% van de patiënten correct als niet-cardiaal danwel cardiaal te classificeren.

In onze vervolg studie (hoofdstuk 5) onderzochten we 72 (73%) van de oorspronkelijke 98 patiënten uit het onderzoek beschreven in hoofdstuk 4, te weten: 39 niet-cardiale en 33 cardiale patiënten. Het onderzoek werd gemiddeld 1,6 jaar na het eerste bezoek aan de behandelend cardioloog uitgevoerd. In deze vervolg studie gaven 35% van de niet-cardiale patiënten aan, dat hun pijn op de borst onveranderd of zelf ernstiger was dan bij het eerste bezoek aan de cardioloog. Bovendien hadden de niet-cardiale patiënten significant minder vitaliteit, meer angst voor hun eigen gezondheid, meer vrees voor lichamelijk letsel dood en ziekte, hogere angst scores en beduidend minder vertrouwen in artsen dan de cardiale patiënten. Uit een logistische regressie analyse op alle variabelen bleek dat de variabelen angst voor eigen gezondheid, spankracht en vrees voor lichamelijk letsel, dood en ziekte voldoende waren om 75% van de patiënten correct als niet-cardiaal danwel cardiaal te classificeren.

In hoofdstuk 6 werd nader ingegaan op de psychologische factoren die gerelateerd zijn aan niet-cardiale pijn op de borst. Bij deze studie werd gebruik gemaakt van de gegevens van onze eerste empirische studie (hoofdstuk 3). Met behulp van LISREL werden de relaties tussen de belangrijkste discriminerende variabelen van niet-cardiale pijn op de borst, hyperventilatie, angst, depressiviteit, somatisatie en leeftijd, voor zowel de niet-cardiale als de cardiale patiënten onderzocht. Hierbij bleek dat in de niet-cardiale groep, angst en somatisatie significant bijdragen aan de mate van hyperventilatie, terwijl in de cardiale groep somatisatie angst en depressie veroorzaakt.

In hoofdstuk 7 worden de overeenkomsten en de verschillen tussen de drie empirische studies besproken.

Samenvattend kan als belangrijkste conclusie van ons onderzoek worden gesteld, dat het tot in hoge mate van nauwkeurigheid mogelijk is om niet-cardiale van cardiale patiënten te onderscheiden op basis van louter psychologische kenmerken. Overeenkomstig de meeste in de literatuur genoemde vervolgstudies, laat onze vervolgstudie zien dat de psychologische morbiditeit hoog blijft, zelfs nadat de niet-cardiale patiënt door de cardioloog gerustgesteld is met "er is niets aan de hand". Wij zouden daarom een sneller verwijsbeleid naar een psycholoog of psychiater willen bepleiten, waarbij de cardioloog gebruik kan maken van de ontwikkelde vragenlijst.

Sneller verwijzen is juist daarom zo belangrijk om somatische fixatie te voorkomen, kosten te besparen en tenslotte, maar niet minder belangrijk, patiënten baat kunnen hebben bij (psycho)therapie.

Het nut van de ontwikkelde lijst zal zich uiteindelijk in de praktijk door middel van een grote studie moeten bewijzen.

# A. Logistic regression analysis

## A.1 Introduction

Predicting whether an event will or will not occur, as well as identifying the determinants significantly contributing to that predicting, is of great interest in medical as well as psychological studies. In the studies of this doctoral thesis, for instance, the main question is whether a patient's chest pain is of a somatic nature or not and which psychological determinants significantly contribute to the successful prediction of the non-cardiac chest pain.

For such kind of data and questions, multivariate logistic regression models can be used. Multivariate logistic regression quantifies the joint association between explanatory variables and the outcome. A mathematical function, i.e. logistic function, is used to describe the association of the determinants on the on hand and the probability of the outcome (value) on the other. The importance of the individual determinants is indicated by regression coefficients to be estimated from the data.

Once the logistic model has been fitted to the data, the estimated probability of a certain outcome can be calculated for each individual patient from the regression coefficients and the respective determinants.

### A.1.1 The logistic regression model

Given the determinants one can directly estimate the probability of an event occurring. When more than one determinant significantly contributes to the model, it can be written as

$$P(event) = \frac{e^R}{1+e^R}$$

or equivalently,

$$P(event) = \frac{1}{1+e^{-R}}$$

where R is the linear combination and $\beta_1$ to $\beta_p$ are the estimated coefficients for the respective variables $X_1$ to $X_p$.

$$R = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p$$

**Figure A.1** *Logistic curve*

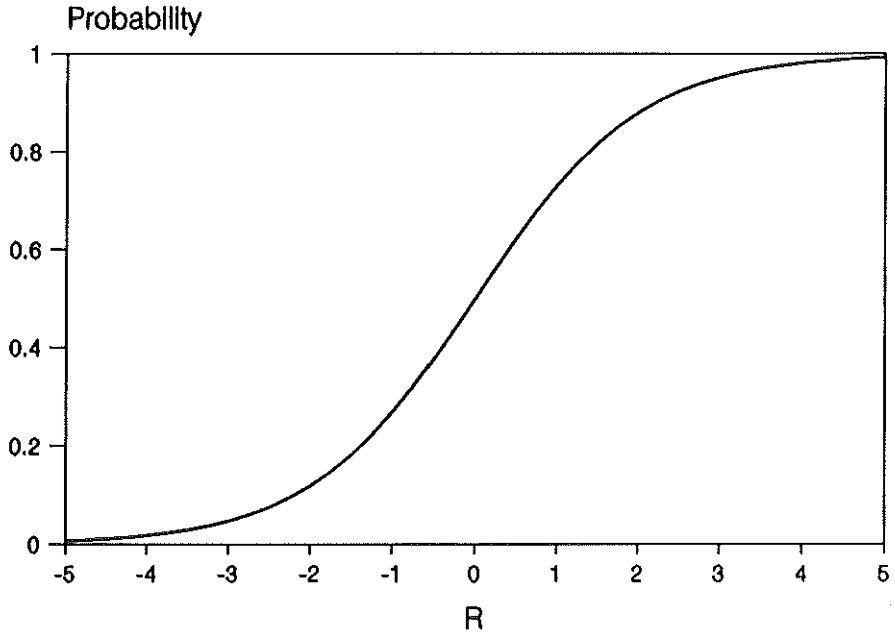



Figure A.1 is a plot of a logistic regression curve when the values of R are between -5 and +5. As can be seen the curve is S-shaped. The relationship between the determinants and the probability is non-linear. Because of the exponentional function in the algebraic formula, the probability of an event occurring will have a value between 0 ($R = -\infty$) and 1 ($R = \infty$).

Parameters of the model are estimated by using the maximum-likelihood method, in that the coefficients that make the observed results most 'likely' are selected. As the logistic regression model is nonlinear an iterative algorithm is necessary for parameter estimation.

**Table A.1** *Parameter estimated for the logistic regression model*

| Variable | $\beta$ | S.E. | df | Sig | Exp ($\beta$) |
|---|---|---|---|---|---|
| Anxiety (ANX) | 1.40 | 0.53 | 1 | 0.008 | 4.04 |
| Hyperventilation (HYP) | 1.33 | 0.42 | 1 | 0.002 | 3.76 |
| Medical Information (MI) | -0.62 | 0.27 | 1 | 0.021 | 0.54 |
| Hyperchondria index (HI) | 0.58 | 0.29 | 1 | 0.043 | 1.79 |
| Invalidity (INVAL) | -0.93 | 0.32 | 1 | 0.003 | 0.40 |
| STAI state (STATE) | -0.77 | 0.34 | 1 | 0.024 | 0.46 |
| Constant | 0.70 | 0.26 | 1 | 0.636 | |

### A.1.2 Estimated coefficients

Table A.1 contains the estimated coefficients ($\beta$) and related statistics from the logistic regression model that predicts non-cardiac chest pain, derived from the data of our comparative study (chapter 3). For understanding the meaning of the estimated coefficient the equation of the logistic model can best be rewritten in terms of the odds of an event occurring.

$$\log\left(\frac{P(non\text{-}cardiac)}{P(cardiac)}\right) = \beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p$$

As log odds are difficult to interpret, it is easier to work with odds. The logistic equation can be written in terms of odds as

$$\frac{P(non\text{-}cardiac)}{P(cardiac)} = e^{\beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p} = e^{\beta_0}\, e^{\beta_1 X_1} \ldots e^{\beta_p X_p}$$

Where $e$ raised to the power $\beta_i$ is the factor by which the odds change when the $i^{th}$ determinant increases by one unit. If $\beta_i$ is positive this factor will be greater than 1, which means that the odds are increased; if $\beta_i$ is negative the factor will be less than 1, which means that the odds are decreased. When $\beta_i$ is 0 the factor equals 1, which leaves the odds unchanged. The odds are shown in the Exp ($\beta$) column. The standard error (s.e.), as a measure of precision, can be used to compute the 95% confidence intervals ($\log(\beta \pm (1.96 \times \text{s.e.}))$).

Non-cardiac chest pain is predicted from a constant and the determinants SCL-anxiety (ANX), hyperventilation (HYP), search for medical information (MI), hypochondria index (HI), physical invalidity (INVAL) and state anxiety (STATE) of the STAI (age and gender are disregarded in this example). All variables have been transformed into z-scores, as we are interested in the relative importance of the determinants.

Given the coefficients ($\beta$), shown in table A.1, the logistic regression equation for the probability of non-cardiac chest pain can be written as

$$P(NCA) = \frac{1}{1+e^{-R}}$$

where

$$R = 0.70 + 1.40(ANX) + 1.33(HYP) - 0.62(MI) + 0.58(HI) - 0.93(INVAL) - 0.77(STATE)$$

Applying the model to the *non-cardiac* patient X, having the following z-scores for the variables ANX=1.78, HYP=2.15, MI=0.05, HI=0.02, INVAL=1.45, STATE=1.39, we find

$$R = 0.70 + 1.40(1.78) + 1.33(2.15) - 0.62(0.05) + 0.58(0.02) - 0.93(1.45) - 0.77(1.39) = \mathbf{3.61}$$

$$P(NCA) = \frac{1}{1 + e^{-3.61}} = 0.97$$

Based on this estimate patient X has a probability of 0.97 of having complaints of a non-cardiac nature.

When applying the model to the *cardiac* patient Y, having the following z-scores for the variables ANX=-0.78, HYP=-0.96, MI=0.05, HI=-0.18, INVAL=0.56, STATE=0.57, we find

$$R = 0.70 + 1.40(-0.78) + 1.33(-0.96) - 0.62(0.05) + 0.58(-0.18) - 0.93(0.56) - 0.77(0.57) = \mathbf{-2.75}$$

$$P(NCA) = \frac{1}{1 + e^{-2.75}} = 0.04$$

Based on this estimate patient Y has a probability of 0.04 of having complaints of a non-cardiac nature, implying that the patient's complaints are of a cardiac nature.

### A.1.3 Goodness of fit

An indication of the goodness-of-fit of the model is the significance level for each variable as found in table A.1 under the column 'Sig'. Except for any confounder variables, all variables should significantly contribute to the model (i.e. $p < 0.05$).

### A.1.4 Performance

There are various ways to assess the performance of the model. One of the most straightforward ways, is to compare the predicted outcomes, by default, dichotomised at $p=0.50$, to the observed outcomes, as can be seen in Table A.2. For each predicted group, all the table shows is whether the estimated probability is greater or less than one-half.

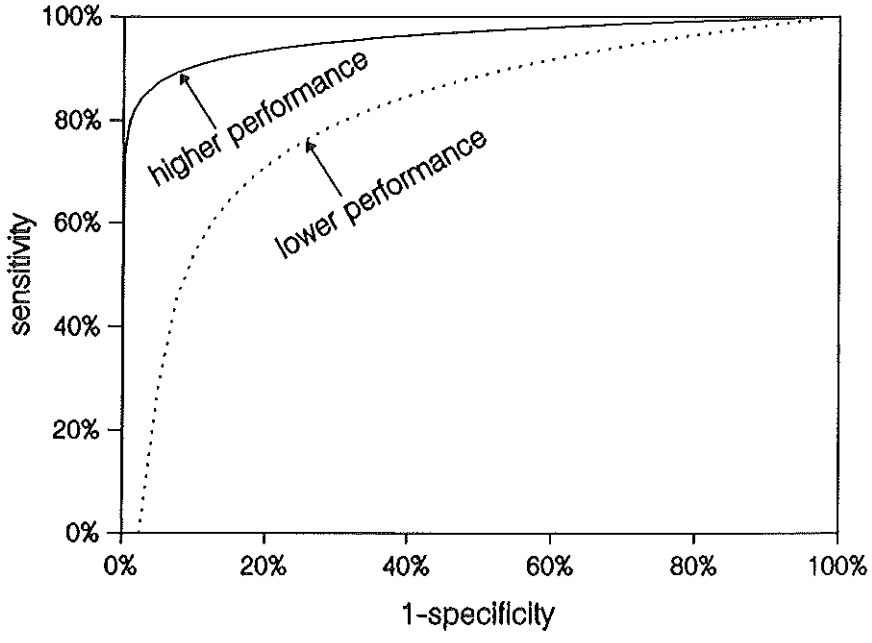
**Table A.2** *Classification table for the cardiac diagnosis (CAD/NCA)*

| | Predicted | | |
|---|---|---|---|
| Observed | CAD ($p<0.50$) | NCA ($p>0.50$) | Percent correct |
| CAD | a 32 | b 15 | 68.1% |
| NCA | c 13 | d 54 | 80.6% |
| | | Overall | 75.4% |

Here 32 (68.1%) patients with coronary artery disease (CAD) were correctly predicted by the model. Similarly 54 (80.6%) of the patient with normal coronary arteries were correctly predicted by the model. For the CAD group 15 (31.9%) patients were incorrectly classified and 13 (19.4%) in the NCA group. Overall 75.4% ((32+53)/114) of the patients were correctly classified as being either CAD or NCA. One of the limitations with this method of examining whether the model depicts 'reality' is that the table does not reveal the distribution of estimated probabilities for the two groups.

The performance of the constructed model can also be measured with a receiver-operator characteristic (ROC) curve. With the logistic model the predicted probability of being a non-cardiac patient for all subjects can be calculated. Subsequently sensitivity (a/(a+b)) and specificity (d/(c+d)) are calculated (see table A.2), which are then used for the ROC curve. In the ROC curve, the true-positive rate (sensitivity) is plotted against the false-positive rate (1 - specificity).

**Figure A.2** *Performance of the model by means of ROC curves*




The discriminative ability of a test is shown by the position of the full curve: the farther upward and to the left the curve lies in the figure, the more optimal the test (see figure A.2). Thus, the area under the ROC-curve reflects the performance of the model, in a sense that a larger surface area reflects a higher performance (1).

### A.1.5 Variable selection

There are different ways of selecting the determinants significantly contributing to the model. With the forward selection method the model starts without

any variables in the model. At each step the variable with the smallest significance level, provided that it is less than the chosen cutoff value (i.e. $p < 0.05$) is entered into the model. With the backward elimination method all variables are entered at the start. At each step variables are evaluated for entry and removal. The likelihood-ratio statistic is then used to remove variables leaving the most significant variables in the model.

## A.2 Reference

1. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143(1):29-36.

# B. Basic principles of structural equation modelling

*H.J. Duivenvoorden and A.W. Serlie*

## B.1 Introduction

In chapter 6 we had a closer look at the variables closely associated to non-cardiac chest pain; hyperventilation, anxiety, depression, somatisation and age, using the structural equation modelling technique LISREL. In this appendix we will describe in more detail the LISREL technique.

Structural equation modelling deals with detecting and testing models for structures of functional relationships between observed (manifest) and unobserved (latent) variables. These relationships are represented in terms of parameters (partial regression coefficients). The kind of relationships may be both direct and indirect (mediated by other variables).

The structure of the hypothesized model can be visualized by a path diagram in which the functional relationships are 'translated' by means of unidirectional and bidirectional arrows at the dependent variables (outcome variables, response variables), and only bidirectional arrows at the independent variables. Structural hypotheses can be tested by constraining single parameters, across different parameters and across samples.

Constraints on single parameters concern fixing parameters to e.g. 1.0, while on different parameters constraints of equality may be desired, e.g. when the same variables are measured repeatedly. Across samples (e.g. comparing a hypothesized model for men and women) equality constraints may be needed.

Usually in the psychological sciences observed variables are not measured without errors. That is why latent variables are of utmost importance. Scores on latent variables are equal to scores on observed variables minus measurement error.

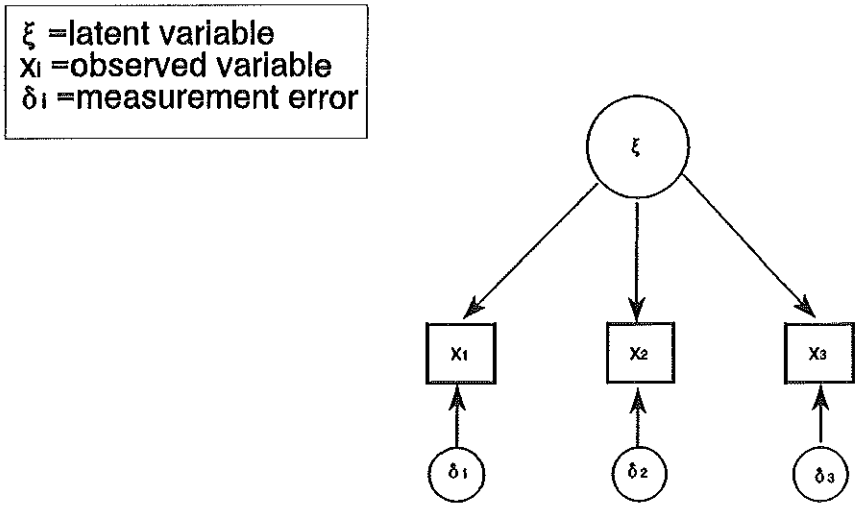
It is of eminent importance to have (thorough) ideas, thoughts or hypotheses about the structure of the functional relationships between the variables: the more specific the set of hypotheses, the more stringent testing will be.

An excellent introduction on structural equations with latent variables is written by Bollen (1).

## B.2 Elements of structural equation models

The general structural equation model consists of two parts: 1. the measurement model, of which factor analysis is well-known in psychology, and 2. the structural model, that deals with the relationship between the independent and dependent variables. Structural equating modelling can be used for ANOVA testing, testing by means of multiple regression, factor analysis and other techniques, but it is often difficult to test hypotheses that do not fit these techniques.

**Figure B.1** *measurement model; square: observed variable; large circle: latent variable and small circle: measurement error. Unidirectional arrows represent directional relationship*



### B.2.1 Measurement model

Measurement models are concerned with the relationships between observed and latent variables. A simple measurement model is shown in Figure B.1.
Two important advantages of this model have to be mentioned:

1. Explicit acceptance of measurement error (i.e. random error, uniqueness) in the model. Each of the three squares represent indicators of the observed variable x; measurement error ($\delta$) is represented by a circle connected to the square by an unidirectional arrow. That the measurement error is represented by circles can be explained by the fact that measurement error is not directly observed; it is an unobserved source of variability in the data.
2. Evaluation of the measurement model implies solving several measurement equations: in Figure B.1 each indicator is determined by one latent variable $\xi$ and a latent variable that accounts for the variability unique for the indicator ($\delta_i$, measurement error).

A desirable property of a measurement model is that each latent variable of the model is uniquely and adequately represented by indicators.

### B.2.2 Structural model

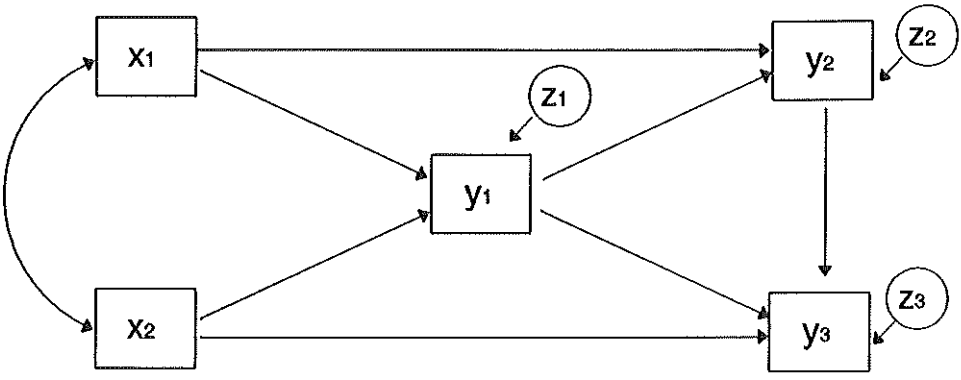
The structural model concerns the relationships between independent and dependent variables, either observed or latent. The bivariate regression is an example of a simple structural model, one in which there is an independent variable and a dependent variable. In Figure B.2 an example of a structural model is visualized in the form of a path diagram.

In this path diagram seen in Figure B.2, all variables, symbolized by squares, are observed: $x_1$ and $x_2$ represent the independent variables and $y_2$ and $y_3$, the dependent variables, while $y_1$ represents the intervening variable.
Some benefits of structural equation modelling are:

1. Like regression analysis, but unlike ANOVA, structural equation modelling impose no constraints on the relationship between independent variables (see Figure B.2; the bidirectional arrows).
2. Structural equation modelling has explicitly the possibility to introduce directional relationships between dependent variables, which is not possible in, either ANOVA, MANOVA, or multiple regression analysis. In Figure

**Figure B.2** *structural model; square: observed variable; and small circle: measurement error; Unidirectional arrows: represent directional relationship; bidirectional arrows: represent non-directional relationship*

$x_i$ = observed independent variable
$y_i$ = observed dependent variable
$z_i$ = error term in structural equation



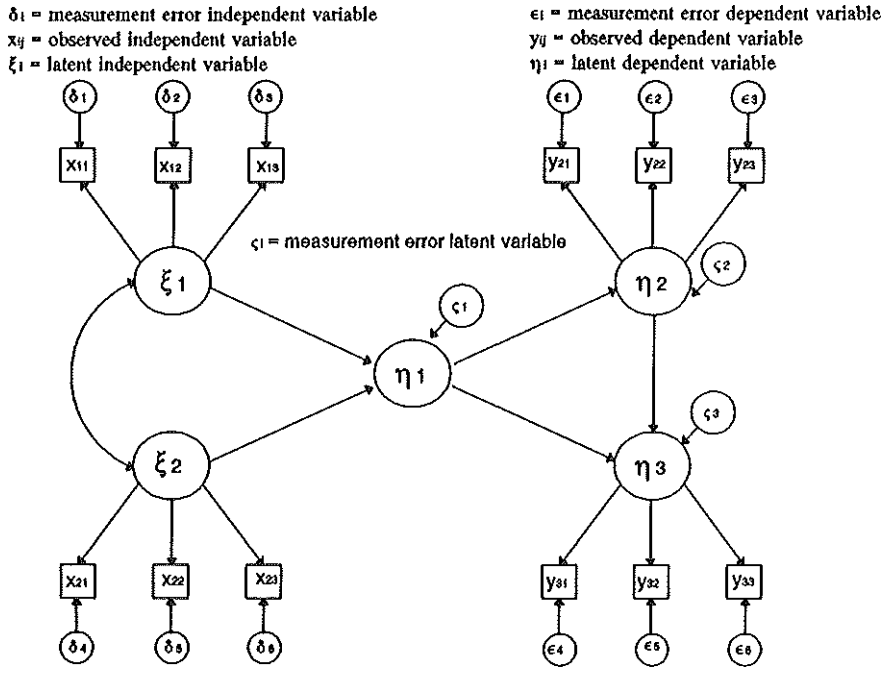

B.2 $y_1$ is both the independent and the dependent variable. There are multiple equations which can be solved simultaneously.

### B.2.3 General structural model

This type of modelling incorporates both the measurement models and the structural equation models. It corrects for unreliability. An illustration is given in Figure B.3.

In Figure B.3 both the independent variables and the dependent variables are represented by large circles indicating that they are latent. The observed variables are represented by squares. The relationships among the variables are not constrained to bivariate correlations such as in factor analysis models. All paths of the model in Figure B.3 are estimated simultaneously. General structural modelling has the quality to solve multiple regression, factor analysis and MANOVA in one single model. Furthermore, there are facilities to test directional relationships between independent on the side and dependent variables on

**Figure B.3** *general structural model; square: observed variable; large circle latent variable; small circle: measurement error. unidirectional arrows: directional relationship; bidirectional arrows: nondirectional*




the other side.

In addition, the total effects of independent on dependent variables can be decomposed in direct and indirect contributions.

## B.3 Estimation

Before a specific theoretical model can be tested on plausibility, one has to answer the question whether the theoretical model is identifiable. This implies that the number of parameters to be estimated has to be lower than the number of nonredundant elements in the covariance matrix of the observed variables. In other words, the number of degrees of freedom has to be greater than 0. If the number of degrees of freedom is positive, then the unknown parameters of the specified theoretical model can be uniquely estimated, such as regression coefficients, variances and covariances under the theoretical model. If the number of degrees of freedom is lower than 0, then the model is underidenti-

fied or not identifiable. That is to say, the parameter estimates cannot be determined uniquely: an infinite number of solutions is possible. In exploratory factor analysis, for example, the undeterminancy can be estimated by the constraint that the factors are orthogonal. The estimation is based on the structure matrix of variances and covariances. In covariance structure analysis the covariances of the observed variables are functions of the unknown parameters to be estimated. A special kind of covariance matrix is the correlation matrix, which is based on standardized variables.

The aim of the estimation method is to minimize the discrepancy between the sample covariance matrix and the theoretical covariance matrix. There are a number of estimation methods, like maximum likelihood and weighted least squares (2). Which estimation method is indicated, depends on level of the variables (ordinal, interval or censored) and on (non)normality of multivariate distribution.

In addition to estimation based on covariance (or correlation) matrices, it is also possible to estimate means, especially of value in case of repeated measurements on the same variables.

The variables included in the model and postulating the relationships of the variables and of the residuals terms constitute the specification of the model. But, a model is misspecified if a important causal variable is omitted or if a causal path is incorrectly omitted.

It is of great importance that the final model, ideally, comprises only statistically significant and theoretically meaningful terms.

### B.3.1 Model fit

Many performance measures have been developed in order to give information about the plausibility of the fitted models.

Tanaka (3) identified six dimensions; 1. is the performance population or sample based: population based fit indices estimate a known population parameter, while sample based indices estimate the model fit in the observed sample; 2. fit indices that favour simple models, penalize more complex models (parsimoniousness); 3. normed (0-1 range) versus nonnormed indices; 4. absolute versus relative fit, the latter being used with a specific model as a reference for other model comparisons; 5. estimation free versus estimation specific method, the latter provide different fit indices across different methods of

estimation; and 6. sample size dependent versus sample size independent fit indices.

Most used measure is the $\chi^2$-test for model fit. Furthermore, goodness-of-fit and adjusted goodness-of-fit as performance measures are frequently used. Worthwhile to mention is the standardized root mean squares of residuals. As a measure for crossvalidation, it makes sense to use Cudeck and Browne's cross-validation index (4) and information theory based on measures like AIC (5, 6) and CAIC (7).

## B.4 Strategy of analysis

Jöreskog and Sörbom (2) distinguish three main strategies:

1. In strictly confirmatory sense one model has been specified and this model will be tested.
2. Several alternative or competing models have been specified. On basis of one single set of empirical data one of these models should be selected as being most plausible.
3. A tentative model has been specified. If the model does not fit, the model should be modified, and tested again on the same data. Re-specifying of models may be theory-based and data-driven. This strategy has the character of model generating rather than model testing.

## B.5 References

1. Bollen KA. Structural equations with latent variables. New York: Wiley, 1989: 514. .
2. Jöreskog K, Sörbom D. LISREL 8: Structural equation modeling with the simplis command language. Chicago: Scientific Software International, Inc., 1993. .
3. Tanaka JS. Multifaceted conceptions of fit in structural models. In: Bollen KA, Scott Long J, ed. Testing structural equation models. California: Sage, 1993: 10-39.
4. Cudeck R, Browne MW. Cross-validation of covariance structures. Multivar Beh Res 1983; 18: 147-157.
5. Akaike H. A new look at statistical model identification. In IEEE transactions on automatic control, 1974: 716-723.

6. Akaike H. Factor analysis and AIC. Psychometrika 1987; 52(3): 317-332.
7. Bozdogan H. Model selection and Akaike's Information Criterion (AIC): The general theory and its analytical extensions. Psychometrika 1987; 52(3): 345-370.

# C. Rotterdam Chest Pain Differentiation Questionnaire

Questionnaire derived from the scales significantly contributing to the differentiation between non-cardiac and cardiac chest pain

items 1- 9 Rose Questionnaire (1)
items 10-21 MEGAH: fear for one's own health (2)[1]
items 22-33 HPPQ: disability (3)[1]
items 34-45 FSS: fears related to bodily injury, death and illness (4)
items 46-51 POMS: fatigue (5)

1 Have you had any pain or discomfort in your chest, during the past six months?
O Yes
O No

2 Do you get any pain or discomfort when you walk uphill or hurry?
O Yes
O No
O Never hurry or walk uphill

3 Do you get any pain or discomfort when you walk at an ordinary place on the level?
O Yes
O No
O never walk

4 What do you do if you get any pain or discomfort while you are walking?
O Carry on
O Stop or slow down
O Take nitroglycerine tablet

5 If you stand still, what happens to it?
O Relieved
O Not relieved

6 How soon?
O 10 minutes or less
O More than 10 minutes

---

[1] *Reprinted with permission of the publisher of the MEGAH and the HPPQ, Swets & Zeitlinger BV, Lisse, the Netherlands.*
*Contact the publisher for permission to use the questionnaire for clinical or research purposes: Swets & Zeitlinger BV, Lisse, Swets Testservices, Heereweg 347-B, 2161 CA, Lisse, the Netherlands.*

7 Can you indicate where the pain is located?
- O Sternum (upper or middle)
- O Sternum (lower)
- O Left anterior chest
- O Left arm
- O Other

8 Do you feel it anywhere else?
- O Yes
- O No

9 Where else do you feel the pain?
- O Right chest
- O Right arm
- O Neck or jaws
- O Other

**How much do you agree/disagree with the following statements:**

*1. strongly agree with*
*2. somewhat agree with*
*3. do not agree with, but also do not disagree with*
*4. somewhat disagree with*
*5. strongly disagree with*

| | | | | | | |
|---|---|---|---|---|---|---|
| 10 | When I see or read things about illnesses, I often relate them to myself | 1 | 2 | 3 | 4 | 5 |
| 11 | I regularly feel strange aches and pains in my body | 1 | 2 | 3 | 4 | 5 |
| 12 | I am afraid I may have contracted a serious illness | 1 | 2 | 3 | 4 | 5 |
| 13 | Whenever I feel pain anywhere, I straightaway think of a serious illness | 1 | 2 | 3 | 4 | 5 |
| 14 | I am afraid of incurable illnesses | 1 | 2 | 3 | 4 | 5 |
| 15 | After others have told me about their illnesses and symptoms I check to see if similar symptoms appear with me | 1 | 2 | 3 | 4 | 5 |
| 16 | Whenever there is something wrong with me, I straightaway think of serious disease such as cancer or AIDS | 1 | 2 | 3 | 4 | 5 |
| 17 | At night I often lie awake thinking how vulnerable a person is, with regard to his health. When I consider everything that may go wrong with me, I get very tense and cannot get to sleep. | 1 | 2 | 3 | 4 | 5 |
| 18 | I have trouble visiting people in hospital who have a serious illness: I straightaway relate it to myself | 1 | 2 | 3 | 4 | 5 |
| 19 | I often panic | 1 | 2 | 3 | 4 | 5 |
| 20 | I cannot get rid of the thought that I may have a serious illness | 1 | 2 | 3 | 4 | 5 |
| 21 | I constantly worry about my health | 1 | 2 | 3 | 4 | 5 |

**Do the following statements apply to you?**

| | | |
|---|---|---|
| 22 | If it is cold and windy outside, I hardly ever leave the house . | correct / ? / incorrect |
| 23 | I could do a lot more work formerly . . . . . | correct / ? / incorrect |
| 24 | I do not have enough stamina . . . . . | correct / ? / incorrect |
| 25 | I used to be capable of a lot more . . . . . | correct / ? / incorrect |
| 26 | I tire faster than I think is normal . . . . . | correct / ? / incorrect |
| 27 | I feel tight in the chest quite often . . . . . | correct / ? / incorrect |
| 28 | I still feel up to anything . . . . . | correct / ? / incorrect |
| 29 | Thing often go wrong if I have to do something quickly . . . | correct / ? / incorrect |
| 30 | I tire quickly even if I do not do anything out of the ordinary . | correct / ? / incorrect |
| 31 | I do not like the idea of doing heavy work . . . . . | correct / ? / incorrect |
| 32 | I get out of breath quickly . . . . . | correct / ? / incorrect |
| 33 | I still feel quite capable of taking part in sports . . . . . | correct / ? / incorrect |

**How afraid are you of:**

*1. not at all*
*2. a little*
*3. quite a lot*
*4. a lot*
*5. extremely*

| | | | | | | |
|---|---|---|---|---|---|---|
| 34 | Open wounds . . . . . | 1 | 2 | 3 | 4 | 5 |
| 35 | Dead people . . . . . | 1 | 2 | 3 | 4 | 5 |
| 36 | People with deformities . . . . . | 1 | 2 | 3 | 4 | 5 |
| 37 | Receiving injections . . . . . | 1 | 2 | 3 | 4 | 5 |
| 38 | Seeing other people injected . . . . . | 1 | 2 | 3 | 4 | 5 |
| 39 | Sick people . . . . . | 1 | 2 | 3 | 4 | 5 |
| 40 | Witnessing surgical operations . . . . . | 1 | 2 | 3 | 4 | 5 |
| 41 | Human blood . . . . . | 1 | 2 | 3 | 4 | 5 |
| 42 | Animal blood . . . . . | 1 | 2 | 3 | 4 | 5 |
| 43 | Hospital smells . . . . . | 1 | 2 | 3 | 4 | 5 |
| 44 | Cemeteries . . . . . | 1 | 2 | 3 | 4 | 5 |
| 45 | Doctors . . . . . | 1 | 2 | 3 | 4 | 5 |

**How did you feel over the past few days**

*0. not at all*
*1. a little*
*2. somewhat*
*3. rather*
*4. extremely*

| | | | | | | |
|---|---|---|---|---|---|---|
| 46 | Exhausted | 0 | 1 | 2 | 3 | 4 |
| 47 | Tired | 0 | 1 | 2 | 3 | 4 |
| 48 | Have no strength left | 0 | 1 | 2 | 3 | 4 |
| 49 | Listless | 0 | 1 | 2 | 3 | 4 |
| 50 | Worn out | 0 | 1 | 2 | 3 | 4 |
| 51 | Wearied | 0 | 1 | 2 | 3 | 4 |

**References**

1. Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. Geneva: World health organization, 1982. .
2. Schmidt AJ, Lousberg R. [Health-attitude and hypochondrias: Development of the MEGAH-scale] Gezondheidsattitude en hypochondrie. Ontwikkeling van de Maastrichter eigen gezondheidsattitude en hypochondrie-schaal. Gedrag en Gezondheid 1993; 21(2): 84-94.
3. Erdman RAM, Duivenvoorden HJ, Verhage F, Kazemier M, Hugenholtz PG. Predictability of beneficial effects in cardiac rehabilitation: a randomised clinical trial of psychological variables. J Cardiopulm Rehabil 1986; 6: 206-213.
4. Arrindell WA. Dimensional structure and psychopathology correlates of the Fear Survey Schedule (FSS-III) in a phobic population: A factorial definition of agoraphobia. Behav Res Ther 1980; 18(4):229-242.
5. Wald FDM, Mellenbergh GJ. [The shortened version of the Dutch translation of the Profile of Mood States] De verkorte versie van de Nederlandse vertaling van de Profile of Mood States. Ned Tijdschr Psychol 1990; 45:86-90.

# Acknowledgements

The completion of this thesis would not have been possible without the help of the following persons:

- My promoters Prof. Dr Jan Passchier and Prof. Dr Jos Roelandt, without whose enthusiasm and constant support my research-project would never have resulted in this thesis.
- My co-promoter Dr Ruud Erdman, who introduced me into the fascinating world of psycho-cardiac research and backed me throughout the four years it took to complete the studies of this thesis.
- Dr Hugo Duivenvoorden, who not only was invaluable for the methodology and statistics, but also was a pillar in the realisation of this thesis.
- Dr Folkert ten Cate and Dr Jaap Deckers for their sincere enthusiasm and expert cardiological guidance.
- Dr Mike Scheffer and Dr Jan Panis of St. Clara Hospital Rotterdam for their significant help in setting up and carrying out a study at their cardiology out-patient's clinic.
- All the doctors and employees of the cardiology out-patient's clinic of the Thoraxcentre of the Rotterdam University Hospital, who provided me with patients, coffee, "house-cd's", support and cheerful remarks for the whole duration of the study.
- Special thanks to Ron van Domburg, who provided me with endless lists of patient-information and -selections.
- Robin Peeters for his help in reading all the patient-letters.
- All my former colleagues of the Department of Medical Psychology and Psychotherapy. You all made work a second home. With a certain melancholy I look back at the time spent with the CCC, GEO, lunches and drink drams.
- All those others, who mean so much and make it all worth while: Jantina, Mum and Dad, Siert and Magriet, Anya and Mark, Pieter, the paranymphs and of course all the "Houthakkers".

# Curriculum Vitae

Alexander Willem (Alec) Serlie was born on 5 July 1965 in Vlaardingen. After completing grammar school he studied experimental psychology at Leiden University. He graduated in 1990 on selective visual attention. Following his graduation he worked as a statistical programmer at various non-profit organisations. From 1992 until 1996 he was a research assistant at the Department of Medical Psychology and Psychotherapy of the Erasmus University Rotterdam and at the Department of Cardiology of the Rotterdam University Hospital 'Dijkzigt'. Since 1996 the author is employed at the industrial psychology business unit of GITP International BV in Rotterdam.