# Diagnosis and Prognosis of Cardiac Syndrome X

Ilse Anne Christien Vermeltfoort

The printing of this thesis was financially supported by:
Institute Verbeeten, Research Centre Linnaeus Institute Spaarne Hospital, Lamepro, Actelion, GE healthcare, Covidien, Mediphos Medical Supplies BV, Medrad, Stichting Ina Veenstra-Rademaker

Diagnosis and prognosis of Cardiac syndrome X

ISBN: 9789086595525
Photo: NASA
Cover design and lay-out: Chris Bor, Medical Photography and illustration, Academic Medical Centre, Amsterdam
Printed by: Buijten en Schipperheijn, Amsterdam

VRIJE UNIVERSITEIT

# Diagnosis and Prognosis of Cardiac Syndrome X

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op dinsdag 31 mei 2011 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

**Ilse Anne Christien Vermeltfoort**
geboren te Eindhoven

promotor: prof.dr. G.J.J. Teule
copromotor: dr. P.G.H.M. Raijmakers

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

# CONTENTS

# Chapter 1

# Introduction and outline of the thesis

# 1.1 Introduction and outline of the thesis

As coronary angiography (CAG) became widely practiced in 1960s, it was soon apparent that not all patients with clinical suspicion of coronary artery disease had obstruction of epicardial coronary arteries. It became clear that many patients showed no evidence of obstructive coronary artery disease. These observations were confirmed in larger studies, reporting that up to 20% of the patients, undergoing CAG, had no significant stenosis of the epicardial coronary arteries (1-3). Association with myocardial ischemia, however, remained a possible explanation for the angina, because sometimes it is the abnormal noninvasive test, which leads to the performance of a CAG. This is also the case in a patient with cardiac syndrome X (CSX), participating in the studies as described in this thesis.

## Case study

*A school teacher, age 53, married and two children, was referred because of dyspnoe and severe chest pains during exercise. These complaints started after an episode of fever, presumably due to an upper airway infection. She never experienced chest pains before, although she was used to running on a weekly basis (10 km in 1 hour). She consulted a pulmonologist, who found no explanation for the complaints. The X-thorax and a ventilation perfusion scan showed no abnormalities.*

*During a holiday with her family, the chest pains returned, especially during exercise. She was no longer able to climb hills. Back home, her general practioner described nitroglycerin, which relieved the chest pains.*

*The patient had no cardiac risk factors. Physical examination by a cardiologist was completely normal, as were the routine laboratory test. The resting ECG was normal, during exercise, however, a significant ST-segment depression was documented and the patient again had angina-like chest pain. Myocardial 99mTc-MIBI perfusion SPECT studies during rest and exercise demonstrated a reversible perfusion defect in de anterior mid and anteroseptal mid segments (Fig 1), compatible with ischemia in the LAD region. A CAG was scheduled and a calcium antagonist (Tildiem) was prescribed. Angina symptoms decreased after tildiem (Fig 2).*

In many other CSX patients, the effects of the usual anti-anginal medication are less or inconsistent. Reassurance is important but cannot always prevent emergency room evaluations and repeated catheterizations, with obvious effects on quality of life and health care costs, which according to the Women's Ischaemia Syndrome Evaluation (WISE) study might be $ 1 million for each CSX patient in the USA. CSX therefore is an important health care problem which needs further study, with regard to the epidemiology, the pathogenesis, the diagnosis and prognosis in CSX patients (4).

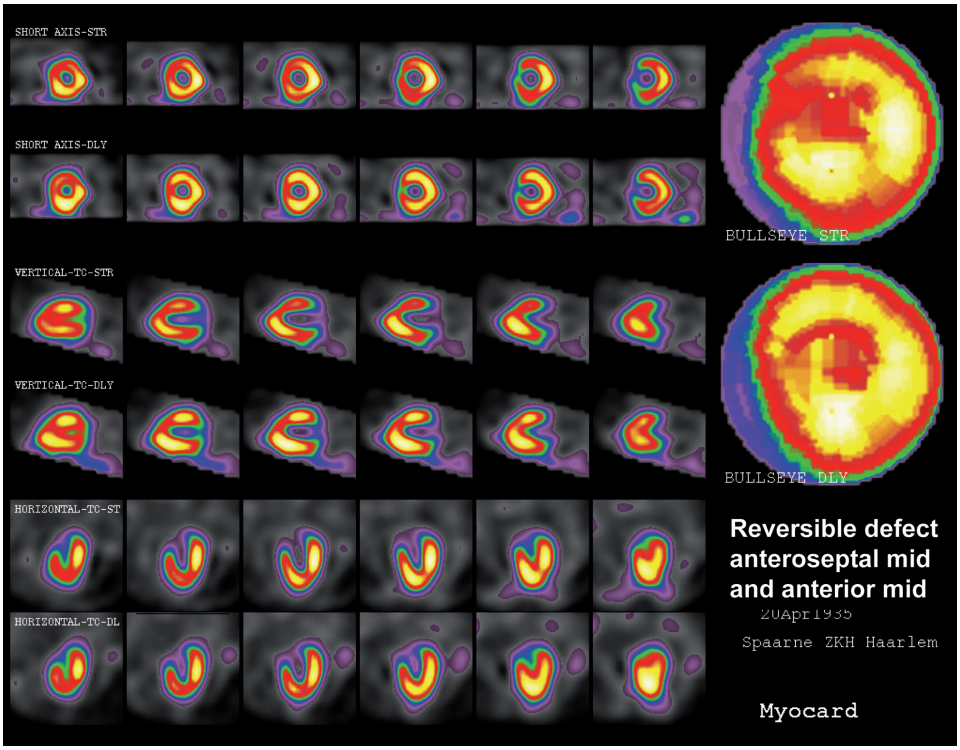



**Fig 1:** Reversible perfusion defect anteroseptal mid and anterior mid.

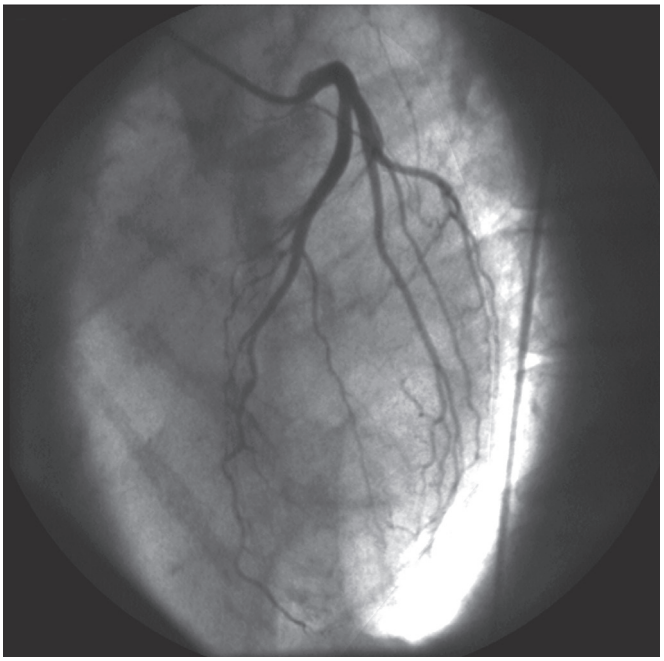


**Fig 2:** Coronary angiography shows a normal left coronary artery

# 1.2. Pathogenesis of cardiac syndrome X

## Coronary microvascular dysfunction

Coronary microvascular dysfunction (CMVD) has been suggested as the cause of angina in a subgroup of CSX patients with reduced CFR and normal coronary arteries (5)**.** Coronary blood flow (CBF) abnormalities related to CMVD may differ substantially from those caused by flow-limiting stenoses in large coronary arteries detected by CAG. (fig 3) In the latter case, the impairment of myocardial perfusion is homogeneously distributed within the myocardial layers perfused by the stenosed artery resulting in detectable segmental perfusion defect.
In contrast, in the case of CMVD, the abnormality may not involve all coronary microvessels of a major coronary branch uniformly but may be distributed in the myocardium in a scattered manner as proposed by Maseri (6). This distribution of focal ischaemia in relatively small myocardial regions can provide a plausible explanation for the difficulties in obtaining objective evidence of myocardial ischemia in most CSX patients when standard diagnostic methods are used.

Hence, diagnostic tests evaluate different functional and anatomical aspects of the heart, the CAG is the gold standard test for evaluation of the coronary arteries but cannot detect microvascular dysfunction. On the contrary, imaging techniques like CMR and SPECT evaluate left ventricular myocardial blood flow, which is downstream of obstructive CAD and microvascular dysfunction. The subendocardium is most susceptible to perfusion impairment and ischaemia occurs in the subendocardium before advancing to the subepicardial layer. Subendocardial perfusion imaging may therefore be an important technique to enhance the sensitivity for detection of myocardial ischaemia.

Positron emission tomography (PET) provided evidence for a reduced coronary vasodilatation and myocardial ischaemia in CSX (7, 8), these results however could not be confirmed by others (9, 10). Similar disagreements occur for functional ischaemia during stress (11).
A number of CMR studies have reported that abnormalities in the function and structure of the coronary microcirculation occur in many clinical conditions, including CSX. An important CMR study suggested the presence of subendocardial hypoperfusion (12) in 20 cardiac syndrome X patients stressed with adenosine. These results suggest a dysfunction of the coronary microcirculation.
Endothelial dysfunction might also be induced by mental stress, anxiety and panic disorders. Mental stress has been linked with impaired myocardial blood flow,

**Fig 3:** Differences in myocardial ischemia caused by a significant coronary stenosis (**A**) or by CMVD (**B**)

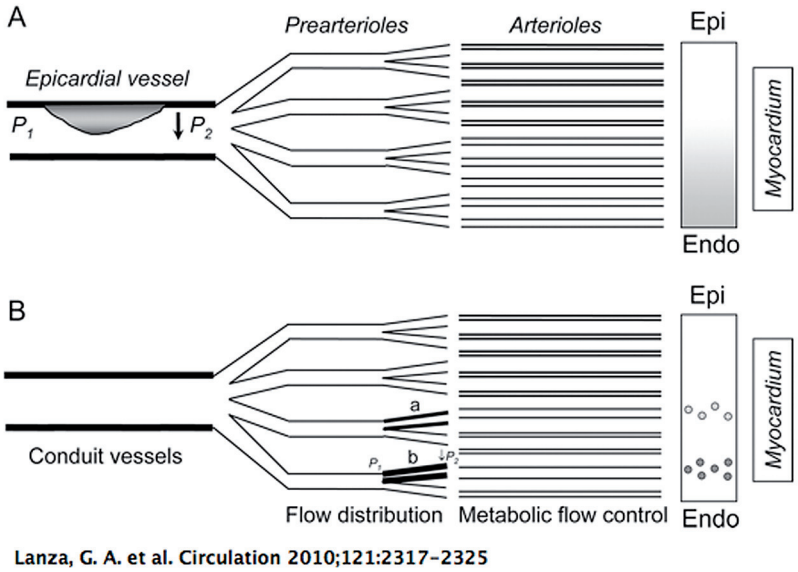



**Fig 3** In the case of an epicardial (Epi) stenosis, myocardial ischemia diffusely involves the whole myocardial (usually subendocardial) territory supplied by the vessel (gray area). In the case of microvascular alterations, myocardial ischemia is likely localized only in small myocardial areas, patchy diffused in the myocardium (small circles); territory. Also in this case, ischemia more easily occurs in subendocardial regions (more intense gray color of the small ischemic areas). Endo indicates endocardial. a and b indicate dysfunctional microvessels; P1 and P2, blood pressure proximal and distal to obstructive vessels

*Reproduced with permission of Circulation*

particularly in the microvascular bed (13, 14). Mental stress can cause vasoconstriction in patients without coronary disease, as in the case of CSX (15, 16). Increased cardiac adrenergic activity can play a significant pathogenetic role in patients with CSX. Severe global or regional abnormalities in cardiac adrenergic innervation are indeed detectable in most patients and can favor coronary microvascular constriction. Other potential causes of coronary microvascular dysfunction, reported in several studies, include increased insulin resistance (17), which may facilitate endothelial activation and dysfunction, estrogen deficiency in women (18), enhanced activity of the membrane sodium-hydrogen exchanger (19), systemic inflammation (20-22) and coronary small vessel viral infection (23).

### Abnormal pain perception

Rosen and Camici studied angina pectoris as a model of visceral pain using PET and $^{15}O$- labeled water for activation studies during pharmacologically-induced ischaemia (24). They obtained a 'map' of cortical activations involved in the perception of angina. Subsequently the difference between painful and silent myocardial ischaemia was investigated (25). It was concluded an abnormal handling of afferent signals by the central nervous system might determine the perception of cardiac pain and provide an explanation for CSX.
In addition, changes in regional cerebral blood flow during dobutamine stress were studied (26). The CSX patients and normal controls had comparable responses to dobutamine, with activations in the hypothalamus, the thalamus, the right frontal cortex and the anterior temporal poles. These responses were associated with the sensation of a fast and powerful heartbeat. In CSX the dobutamine stress also generated chest pain, accompanied by activation in the right anterior insula.
Other studies, using neuromodulation devices (27), spinal cord stimulation (28) and autogenic training - an hypnosis-based relaxation technique (29) - have also suggested that CSX patients have an increased sensitivity to pain.

In summary, several potential causes of coronary microvascular dysfunction have been described, suggesting different, and variously concurrent, pathogenetic mechanisms in individual patients, which can also account for the described heterogeneous pathophysiological features of CSX. Accordingly, it is important to distinguish the syndrome from microvascular dysfunction in association with cardiac or systemic diseases, which can be defined as secondary microvascular angina (MVA) (5). Lanza have recently proposed a new classification of coronary microvascular dysfunction. He suggest to label CSX in the future as stable primary MVA (22).

## 1.3 CSX Diagnosis

The definition of CSX is controversial. Literature reviews usually refer to the classic triple combination of angina pectoris, a normal CAG and noninvasive tests indicating the presence of ischemia. However, intervention CSX studies do not always stick to this classic triple combination. Also important cardiac textbooks like Braunwald describes CSX as the syndrome of only angina and normal CAG ("broad diagnosis") (30). Furthermore, rheumatologic disorders, such as fibromyalgia and costochrondritis, and noncardiac causes of chest pain, such as esophageal dysfunction, have to be excluded as CSX.
The different set of criteria for CSX diagnosis may reflect the heterogeneity of the CSX group.

The largest studies of test characteristics like sensitivity and specificity have been done with gated SPECT. The inter- and intra-observer agreements for SPECT on a large group of patients (n = 138) were 89% and 94%, respectively, employing three experienced readers (31). Another large study (n=108) gave good-to-excellent inter- and intra-observer agreement, with kappa = 0.71 - 0.85 (32).

For CMR the inter- and intra-observer agreement for quantification as been assessed as 55% and 85%, respectively, but the inter-observer agreement improved to 88% when the poor-quality measurements were excluded (48 out of 160 segments (33). Interstudy variability for CMR of 15% was reported.(34). A Dobutamine CMR study with 19 patients showed inter-observer variability between individual and consensus interpretations, with kappa = 0.81 and kappa = 0.70 for wall motion and perfusion, respectively (35).

SPECT and first-pass perfusion CMR results compare favorably with those from ergometric tests. Most SPECT results have a diagnostic specificity close to 90% (32, 36-38). Ergometric test results have a specificity of no more than 85%, and sometimes much less (30, 39).
Furthermore, the accuracy of the exercise-induced ST segment depression for detection of significant obstructive CAD is less for women than for men (30). Hence, CSX diagnosis may also be more difficult for female patients. In the United Kingdom a new guideline called "Chest pain or discomfort of recent onset" has been adopted by the NICE (National Clinical Guidelines Centre for Acute and Chronic Conditions). This recently adopted NICE guideline gives a negative advice on using the stress-ECG for women, owing to its poor sensitivity or difficulties in interpretation.
This new guideline omits the exercise stress test from its diagnostic flowchart. Instead, it advises a calcium score for low pre-test likelihood; an MPS with SPECT/stress echocardiography/first-pass CMR for moderate pre-test likelihood; and an effectively immediate CAG for high pre-test likelihood (40).

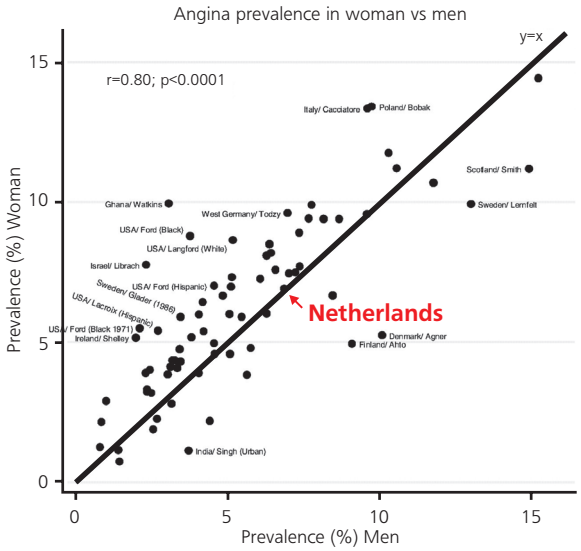
Owing to these test characteristics, there will be angina patients with a false-positive non-invasive imaging test and normal coronary arteries (labeled as CSX). On the other hand, some angina pectoris patients will have a false-negative diagnostic imaging test and are at risk for incorrect diagnosis 'non-cardiac chest pain'. Combining two tests, for example exercise stress testing in combination with SPECT may reduce the false negative rate.

Not only the aforementioned imaging techniques have shortcomings, also observer agreement on angina and CAG interpretation can vary from moderate to excellent (41). The inter- and intra-observer variations for CAG have been specified as 6% and

7%, respectively (42, 43). We have also measured this variation using CAGs from the Spaarne Hospital Heemstede. It is noteworthy that 24% of the reinspected CAGs originally classed as normal were found to show up to 50% luminal stenosis. This discrepancy is partly due to how the CAG results were described: e.g. some observers classified patients with artery wall irregularities as normal. Overall, the agreement about CAG films showing significant stenosis was 100%.

# 1.4 Gender differences and prevalence

The first CSX report by Likoff (1967) included only women with chest pain, positive exercise stress test and normal coronary arteries (44).
Since then it remains stated that the majority of CSX patients are women (45, 46) .
In addition, gender differences exist in the clinical presentation of ischaemic heart disease. One systematic review and meta-analysis on the prevalence of angina in women *versus* men across 31 countries found that women had a slightly higher prevalence of angina compared with men. Angina prevalence using the standardized 7-item Rose angina questionnaire, varied widely across populations, from 0.73% to 14.4% in women and from 0.76% to 15.1% in men, but within each population was gender-related (47).
This female excess in angina pectoris was found across countries with widely differing myocardial infarction mortality rates in women, was particularly high in the American studies, and was higher among nonwhite ethnic groups than among whites.




Hemingway, H et al. Circulation 2008;117:1526-1536

**Fig 4**: Angina prevalence in women vs. men. Labels are given for populations in which the prevalence differs by at least 2.5% between women and men.

*Reproduced with permission of Circulation*

This remarkably consistent female angina excess across countries, spanning 4 decades of study and 4 decades of participant's age is intriguing. Such generalizability suggests an inherent biological basis rather than artifactual explanations. Furthermore there is the paradox of the male preponderance of patients who reach coronary angiography. This suggests a female underuse of cardiac investigation; in the diagnostic work-up women are lost by cardiologists.
Women experience atypical chest pain more often than men, a result that is a challenge to the cardiologist.

Furthermore, the mondial prevalence of CSX in unclear due to racial heterogeneity. As stated in the 'Journal of Health Care for the Poor and the Underserved', there is a higher prevalence of normal coronary angiograms in African Americans with angina compared to whites (48). Indo Asians on the other hand do have smaller coronary arteries compared to Caucasians, owing to the smaller body size (46). Studies in heart transplants and transsexual patients show that large arteries are inherently smaller in women, independent of body size, and such smaller coronary arteries may be associated with ischaemia.
In the Netherlands 298.100 angina pectoris patients were reported on 01-01-2007, consisting of 168200 men (20.8 per 1000) and 129.900 women (15.7 per 1000) (49). It is unknown how many patients had a positive ergometric result and how many of these had normal CAGs, i.e. how many might be categorized as CSX patients. Incidentally, international data on the incidence of CSX are also unavailable or unknown.

# Outline of this thesis



**Chapter 1.** We present a case study of one of our first CSX patients. Introductory remarks on the subject are made and the current ideas on pathogenesis, diagnostic criteria, gender and prevalence are shortly discussed.

**Chapter 2** is a systematic review on the definition of cardiac syndrome X. The effects of using different inclusion and exclusion criteria on CSX incidence and prevalence are described. The criteria are also applied on the 567 patients who underwent a coronary angiography study in the Spaarne Hospital, Haarlem, in 2003.

**Chapter 3.** Endothelial dysfunction might play a role in the pathogenesis of microvascular angina and the endothelin-A receptor is probably involved in CSX patients with mental distress. Blocking this receptor has also shown to be effective in patients with coronary vasospasm, especially when other medication fails. In a patient with coronary vasospasm we studied the effects of bosentan on myocardial perfusion with PET, using $^{15}$O-labeled $H_2O$.

**Chapter 4.** The presumed association between anxiety and the extent of myocardial ischaemia was studied in 20 CSX patients. $^{99m}$Tc Myoview SPECT studies were scored by 3 experienced readers, having no knowledge of the STAI (State-Trait Anxiety Inventory) screening results.

**Chapter 5**. In cardiac syndrome X, the ischaemic origin of reversible perfusion defects is still debated. There are also questions on the reproducibility, the size and the distribution of ischaemic defects in microvascular angina (6). We compared CMR (first-pass perfusion) and standard SPECT in CSX patients.

**Chapter 6.** High resolution imaging with first-pass perfusion CMR suggested the presence of subendocardial hypoperfusion in CSX patients (12).This study asked for confirmation since a new and reliable non-invasive method for microvascular dysfunction was badly needed.

**Chapter 7.** Myocardial blood flow (MBF) measurements with the PET technique and the tracers $^{82}$Rb (Sr-Rb generator), $^{13}$N-labeled NH3 and $^{15}$O-labeled $H_2O$ (both cyclotron products) are the future in the nuclear cardiology. Sensitivity and specificity for ischemia are > 90 % and functional flow reserve can be assessed in quantitative terms. A further improvement might be that endocardial and epicardial perfusion can be measured

separately. The present study in healthy volunteers was designed to provide the normal values for these parameters.

**Chapter 8.** Prognosis in CSX has generally been considered as excellent. A recent study, however, was less optimistic (50). Adverse outcomes, especially in women, had been found. Enough reason for an actual systematic review on incidence and prognosis in CSX, with particular attention for gender.

## Reference List

1. Cannon RO, III. Microvascular angina and the continuing dilemma of chest pain with normal coronary angiograms. *J Am Coll Cardiol* 2009 Sep 1;54(10):877-885.
2. 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 Mar;7(3):479-483.
3. Sharaf BL, Pepine CJ, Kerensky RA, Reis SE, Reichek N, Rogers WJ, et al. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] Study Angiographic Core Laboratory). *Am J Cardiol* 2001 Apr 15;87(8):937-941.
4. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. *J Am Coll Cardiol* 1995 Mar 15;25(4):807-814.
5. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med* 2007 Feb 22;356(8):830-840.
6. Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. *J Am Coll Cardiol* 1991 Feb;17(2):499-506.
7. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Both endothelium-dependent and endothelium-independent function is impaired in patients with angina pectoris and normal coronary angiograms. *Eur Heart J* 1997 Jan;18(1):60-68.
8. Buffon A, Rigattieri S, Santini SA, Ramazzotti V, Crea F, Giardina B, et al. Myocardial ischemia-reperfusion damage after pacing-induced tachycardia in patients with cardiac syndrome X. *Am J Physiol Heart Circ Physiol* 2000 Dec;279(6):H2627-H2633.
9. Camici PG, Marraccini P, Lorenzoni R, Buzzigoli G, Pecori N, Perissinotto A, et al. Coronary hemodynamics and myocardial metabolism in patients with syndrome X: response to pacing stress. *J Am Coll Cardiol* 1991 Jun;17(7):1461-1470.
10. Panza JA, Laurienzo JM, Curiel RV, Unger EF, Quyyumi AA, Dilsizian V, et al. Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. *J Am Coll Cardiol* 1997 Feb;29(2):293-301.
11. Rosen SD, Uren NG, Kaski JC, Tousoulis D, Davies GJ, Camici PG. Coronary vasodilator reserve, pain perception, and sex in patients with syndrome X. *Circulation* 1994 Jul;90(1):50-60.
12. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002 Jun 20;346(25):1948-1953.
13. Arrighi JA, Burg M, Cohen IS, Kao AH, Pfau S, Caulin-Glaser T, et al. Myocardial blood-flow response during mental stress in patients with coronary artery disease. *Lancet* 2000 Jul 22;356(9226):310-311.
14. Yeung AC, Vekshtein VI, Krantz DS, Vita JA, Ryan TJ, Jr., Ganz P, et al. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. *N Engl J Med* 1991 Nov 28;325(22):1551-1556.
15. Lacy CR, Contrada RJ, Robbins ML, Tannenbaum AK, Moreyra AE, Chelton S, et al. Coronary vasoconstriction induced by mental stress (simulated public speaking). *Am J Cardiol* 1995 Mar 1;75(7):503-505.

16. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005 Feb 10;352(6):539-548.

17. Botker HE, Moller N, Ovesen P, Mengel A, Schmitz O, Orskov H, et al. Insulin resistance in microvascular angina (syndrome X). *Lancet* 1993 Jul 17;342(8864):136-140.

18. Kaski JC. Cardiac syndrome X in women: the role of oestrogen deficiency. *Heart* 2006 May;92 Suppl 3:iii5-iii9.

19. Koren W, Koldanov R, Peleg E, Rabinowitz B, Rosenthal T. Enhanced red cell sodium-hydrogen exchange in microvascular angina. *Eur Heart J* 1997 Aug;18(8):1296-1299.

20. Cosin-Sales J, Pizzi C, Brown S, Kaski JC. C-reactive protein, clinical presentation, and ischemic activity in patients with chest pain and normal coronary angiograms. *J Am Coll Cardiol* 2003 May 7;41(9):1468-1474.

21. Lanza GA, Sestito A, Cammarota G, Grillo RL, Vecile E, Cianci R, et al. Assessment of systemic inflammation and infective pathogen burden in patients with cardiac syndrome X. *Am J Cardiol* 2004 Jul 1;94(1):40-44.

22. Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. *Circulation* 2010 Jun 1;121(21):2317-2325.

23. Chimenti C, Sale P, Verardo R, Cicalini S, Petrosillo N, Russo MA, et al. High prevalence of intramural coronary infection in patients with drug-resistant cardiac syndrome X: comparison with chronic stable angina and normal controls. *Heart* 2010 Dec;96(23):1926-1931.

24. Rosen SD, Paulesu E, Frith CD, Frackowiak RS, Davies GJ, Jones T, et al. Central nervous pathways mediating angina pectoris. *Lancet* 1994 Jul 16;344(8916):147-150.

25. Rosen SD, Paulesu E, Nihoyannopoulos P, Tousoulis D, Frackowiak RS, Frith CD, et al. Silent ischemia as a central problem: regional brain activation compared in silent and painful myocardial ischemia. *Ann Intern Med* 1996 Jun 1;124(11):939-949.

26. Rosen SD, Paulesu E, Wise RJ, Camici PG. Central neural contribution to the perception of chest pain in cardiac syndrome X. *Heart* 2002 Jun;87(6):513-519.

27. Jessurun GA, Hautvast RW, Tio RA, DeJongste MJ. Electrical neuromodulation improves myocardial perfusion and ameliorates refractory angina pectoris in patients with syndrome X: fad or future? *Eur J Pain* 2003;7(6):507-512.

28. Sgueglia GA, Sestito A, Spinelli A, Cioni B, Infusino F, Papacci F, et al. Long-term follow-up of patients with cardiac syndrome X treated by spinal cord stimulation. *Heart* 2007 May;93(5):591-597.

29. Asbury EA, Kanji N, Ernst E, Barbir M, Collins P. Autogenic training to manage symptomology in women with chest pain and normal coronary arteries. *Menopause* 2009 Jan;16(1):60-65.

30. libby, bonow, mann, zipes. *Braunwald's Heart Disease*. 8 ed. 2008.

31. Golub RJ, Ahlberg AW, McClellan JR, Herman SD, Travin MI, Mather JF, et al. Interpretive reproducibility of stress Tc-99m sestamibi tomographic myocardial perfusion imaging. *J Nucl Cardiol* 1999 May;6(3):257-269.

32. Johansen A, Gaster AL, Veje A, Thayssen P, Haghfelt T, Holund-Carlsen PF. Interpretive intra- and interobserver reproducibility of rest/stress 99Tcm-sestamibi myocardial perfusion SPECT in a consecutive group of male patients with stable angina pectoris before and after percutaneous transluminal angioplasty. *Nucl Med Commun* 2001 May;22(5):531-537.

33. Muhling OM, Dickson ME, Zenovich A, Huang Y, Wilson BV, Wilson RF, et al. Quantitative magnetic resonance first-pass perfusion analysis: inter- and intraobserver agreement. *J Cardiovasc Magn Reson* 2001;3(3):247-256.

34. Sadeghi MM, Glover DK, Lanza GM, Fayad ZA, Johnson LL. Imaging atherosclerosis and vulnerable plaque. *J Nucl Med* 2010 May 1;51 Suppl 1:51S-65S.

35. Syed MA, Paterson DI, Ingkanisorn WP, Rhoads KL, Hill J, Cannon RO, III, et al. Reproducibility and inter-observer variability of dobutamine stress CMR in patients with severe coronary disease: implications for clinical research. *J Cardiovasc Magn Reson* 2005;7(5):763-768.

36. Golub RJ, Ahlberg AW, McClellan JR, Herman SD, Travin MI, Mather JF, et al. Interpretive reproducibility of stress Tc-99m sestamibi tomographic myocardial perfusion imaging. *J Nucl Cardiol* 1999 May;6(3):257-269.

37. Verzijlbergen JF, Cramer MJ, Niemeyer MG, Ascoop CA, Van der Wall EE, Pauwels EK. ECG-gated and static technetium-99m-SESTAMIBI planar myocardial perfusion imaging: a comparison with thallium-201 and study of observer variabilities. Am J Physiol Imaging 1990;5(2):60-67.

38. Libby, Bonow R, Mann D, Zipes D, Braunwald E. Braunwald's heart disease. 8 ed. 2010.

39. Froelicher VF, Lehmann KG, Thomas R, Goldman S, Morrison D, Edson R, et al. The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. Veterans Affairs Cooperative Study in Health Services #016 (QUEXTA) Study Group. Quantitative Exercise Testing and Angiography. Ann Intern Med 1998 Jun 15;128(12 Pt 1):965-974.

40. (http://www.nice.org.uk/nicemedia/pdf/ChestPainFullGuidelineSection11.pdf. 2011.

41. Christensen HW, Haghfelt T, Vach W, Johansen A, Hoilund-Carlsen PF. Observer reproducibility and validity of systems for clinical classification of angina pectoris: comparison with radionuclide imaging and coronary angiography. Clin Physiol Funct Imaging 2006 Jan;26(1):26-31.

42. Birnbaum LM, Filion KB, Joyal D, Eisenberg MJ. Second reading of coronary angiograms by radiologists. Can J Cardiol 2006 Dec;22(14):1217-2221.

43. Picano E, Parodi O, Lattanzi F, Sambuceti G, Andrade MJ, Marzullo P, et al. Assessment of anatomic and physiological severity of single-vessel coronary artery lesions by dipyridamole echocardiography. Comparison with positron emission tomography and quantitative arteriography. Circulation 1994 Feb;89(2):753-761.

44. Likoff W, Segal BL, Kasparian H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. N Engl J Med 1967 May 11;276(19):1063-1066.

45. Phan A, Shufelt C, Merz CN. Persistent chest pain and no obstructive coronary artery disease. JAMA 2009 Apr 8;301(14):1468-1474.

46. Chaudhary, Kaski, Saperia. Cardiac syndrome X: angina pectoris and normal coronary arteries;up-to-date. 2011.

47. Hemingway H, Langenberg C, Damant J, Frost C, Pyorala K, Barrett-Connor E. Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. Circulation 2008 Mar 25;117(12):1526-1536.

48. Potts JL. Diagnosis and therapeutic intervention in the management of coronary artery disease in African Americans. J Health Care Poor Underserved 1997 Aug;8(3):285-291.

49. (http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/hartvaatstelsel/coronaire-hartziekten/omvang/. 2011.

50. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 2009 May 11;169(9):843-850.

# Chapter 2

Clinical Research in Cardiology 2010 Aug;99(8):475-81

# Definitions and incidence of cardiac syndrome X: review and analysis of clinical data

I.A.C. Vermeltfoort[1], P.G.H.M. Raijmakers[1], I.I. Riphagen[2], D.A.M. Odekerken[3], A.F.M. Kuijper[3], A. Zwijnenburg[4], G.J.J. Teule[5]

1. Department of Nuclear Medicine & PET Research, VU University Medical Centre, Amsterdam, The Netherlands
2. Unit for Applied Clinical Research, Medical Faculty, Norwegian University of Science and Technology, Trondheim, Norway
3. Department of Cardiology, Spaarne Hospital, Hoofddorp, The Netherlands
4. Department of Nuclear Medicine, Spaarne Hospital, Hoofddorp, The Netherlands
5. Department of Nuclear Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

# ABSTRACT



There is no consensus regarding the definition of cardiac syndrome X (CSX). We systematic reviewed recent literature using a standardized search strategy. We included 57 articles. A total of 47 studies mentioned a male/female distribution. A meta-analysis yielded a pooled proportion of females of 0.56 (n=1934 patients, with 95% confidence interval: 0.54-0.59). Nine different inclusion criteria and forty-three exclusion criteria were found in the 57 articles. Applying these inclusion- and exclusion criteria upon a population with normal coronary angiograms treated in one year at a general hospital, the attributable CSX incidence varied between 3% and 11%. The wide range of definitions has large affects on the incidence. This shows the need for a generally accepted definition of CSX.

# INTRODUCTION

The syndrome of angina pectoris with a normal coronary arteriogram, often termed cardiac syndrome X (CSX) is an important clinical entity. (1) About 20 % of patients with anginal chest pain have normal coronary angiograms (CAG). Some physicians regard this as sufficient to diagnose CSX, the so-called broad diagnosis of CSX. (1, 2) However, the cause of CSX is not conclusively established and its definition is controversial. For example, a subgroup of these patients has objective signs of ischaemia, such as the classic downsloping ST-segment depression on exercise testing and/or a reversible defect detected by myocardial single-photon emission computed tomography (SPECT). Consequently, other authorities consider that CSX is discounted by a positive result from any diagnostic test for ischaemia, especially SPECT; and there is also the view that CSX might best be relabelled as one of several causes of microvascular dysfunction. (3) Furthermore, there are various exclusion criteria, such as hypertension and diabetes, that may or may not be used to discount the diagnosis of CSX. Finally, in overviews and textbooks it is often stated that (pre menopausal) women are especially prone for developing cardiac syndrome X. Indeed, some authors exclusively study female patient populations but there is considerable variation in the proportion of women in other studies of CSX patients.

The present paper is a review to determine the gender and main definitions for CSX in the recent literature and also the effects of different definitions upon the attributable CSX incidence. To study this latter aspect we examined and analyzed the CAG data for a population of patients treated in a general hospital in the Netherlands.

# METHODS

## CSX definitions

The PubMed database was used to identify papers in which criteria and definitions for CSX are described. Our search consisted of '(cardiac syndrome x[tiab]) NOT (case reports[pt] OR comment[pt] OR review[pt])', with limits set to English language, humans, and publication date between June 2003 and July 2008. We limited our search strategy to cardiac syndrome X and excluded metabolic syndrome X and tako-tsubo cardiomyopathy. (4-6)

This search yielded 112 references. Conference abstracts, pediatric papers, and 'epublications ahead of print' were excluded. Of 83 articles the full text was retrieved for further analysis. Articles were independently surveyed by 2 authors (IV and GT) and reviewed with regard their used definition of CSX. For this review remained 57 studies.

## Impact of CSX definition upon CSX incidence

All the CAGs made in 2003 in a large general hospital in the Netherlands were collected. An extensive search was made to obtain the clinical history, physical examination, routine laboratory tests and echocardiography results for all patients with CAGs stated to be completely normal. All CAGs were independently evaluated by two experienced observers (AK, DO).



Only patients with original angiograms and sufficient clinical data were included in the present study.

**TABLE 1:** inclusion criteria for CSX

| Inclusion criteria for CSX | Number of studies |
|---|---|
| Angina pectoris | 18 |
| Positive exercise stress test | |
| Normal coronary arteries | |
| Effort induced angina pectoris | 17 |
| Positive exercise stress test | |
| Normal coronary arteries | |
| Angina pectoris | 11 |
| Positive exercise stress test OR positive SPECT | |
| Normal coronary arteries | |
| Angina pectoris | 4 |
| Normal coronary arteries | |
| Angina pectoris | 4 |
| Positive exercise stress test AND positive SPECT | |
| Normal coronary arteries | |
| Angina pectoris | 1 |
| Positive exercise stress test | |
| No significant CAD on CAG, | |
| Effort induced AP | 1 |
| Positive exercise stress test | |
| Normal coronary arteries AND prolonged coronary flow on CAG | |
| Angina pectoris | 1 |
| Positive exercise stress test | |
| Normal coronary arteries AND reduced LVEF on echo | |
| Angina pectoris | 1 |
| Positive SPECT | |
| Normal coronary arteries | |

CSX= cardiac syndrome X, AP=angina pectoris, CAG= coronary angiogram, SPECT=single photon emission tomography, LVEF= left ventricular ejection fraction

# RESULTS

## SX definitions

The 57 papers selected for determining the main definitions of CSX covered a total of 2375 patients. A normal coronary angiogram was used in the majority of the studies. However, in a few studies minimal coronary artery disease, like atheromatous plaque without critical obstructions, is included as "normal coronary angiogram". (7-9) A few studies state in the exclusion criteria minimal coronary artery disease. (10) But in the majority of the studies there was no statement regarding minimal artery disease. Only a few studies specified the interpretation of the normal coronary angiograms, like revision of the CAG films, blinded observation or interpretation by more reviewers.
Table 1 lists the nine CSX definitions, and hence inclusion criteria, obtained from our review of the 57 studies. Table 1.

In more detail:

- Out of 57 studies 42 required positive exercise electrocardiograms for the diagnosis of CSX. The general criterion, when given, for a positive exercise stress test result was uniform ST depression ≥ 1 mm. Only one study considered stress-induced angina without significant ST depression to be positive for ischaemia. (11)
- As much as 11 studies regarded positive myocardial perfusion images to be good alternatives to a positive result from exercise testing.
- As much as 18 studies considered effort-induced angina pectoris as an inclusion criterion
- Four studies defined CSX simply as angina pectoris and normal CAG, the so-called broad diagnosis of CSX.

Table 2 lists no less than forty-three exclusion criteria for CSX. The most frequently used exclusion criteria are valvular heart disease, diabetes mellitus, left ventricular hypertrophy, hypertension and cardiomyopathy. Table 2

**TABLE 2:** Exclusion criteria included studies

| Exclusion criteria used in the studies for present review | N studies of 57 total |
|---|---|
| Valvular heart disease | 33 |
| Diabetes mellitus | 32 |
| Left ventricular hypertrophy | 26 |
| Hypertension | 24 |
| Cardiomyopathy (non specified) | 23 |
| Renal failure | 22 |
| History of myocardial infarction | 15 |

**TABLE 2:** *Cont.*

| Exclusion criteria used in the studies for present review | N studies of 57 total |
|---|---|
| LV dysfunction | 14 |
| Coronary spasm | 13 |
| Hepatic dysfunction | 12 |
| Arrhytmias | 9 |
| Inflammatory disease | 9 |
| Dyslipidaemia | 8 |
| Left bundle branch block | 8 |
| Cardiac disease (non specified) | 7 |
| Gastro Intestinal disorder | 7 |
| Systemic disease (non specified) | 6 |
| Smoking | 6 |
| Thyroid dysfunction | 5 |
| Obesitas | 5 |
| Non-cardiac chest pain | 5 |
| Condunction disorder (incl LBTB) | 5 (13) |
| Hypertrophic CMP (total CMP) | 5 (23) |
| Congestive CMP (total CMP) | 5 (23) |
| Dilated CMP (CMP total) | 4 (23) |
| Alcoholism | 4 |
| Metabolic syndrome | 4 |
| Dysphagia/ oesophagitis | 3 |
| Malignancy | 3 |
| LVEF<40% | 2 |
| Psychiatric ilness | 2 |
| Auto immune disease | 2 |
| Estrogen replacement therapy | 2 |
| PTCA/CABG in history | 2 |
| Ectasia on CAG | 2 |
| Bridging on CAG | 2 |
| Claudicatio intermittens | 2 |
| Heart failure ( non specfied) (total) | 1 (17) |
| Myocarditis | 1 |
| Congenital heart disease | 1 |
| Aortic wall diseases | 1 |
| Anaemia | 1 |
| Thrombocytopenia | 1 |

In overviews and textbooks it is often stated that (pre menopausal) women are especially prone for developing cardiac syndrome X.
In Table 3 data of the individual studies are presented. Table 3
In 53 out of the total of 57 included studies the female/male distribution of the study population was mentioned. Six studies were focused upon female patients with CSX. These studies were excluded for the pooling of the proportion of women in the study populations. Ultimately 47 studies with a total of 1, 934 patients could be used for the meta-analysis.

**TABLE 3:** included studies of CSX patients

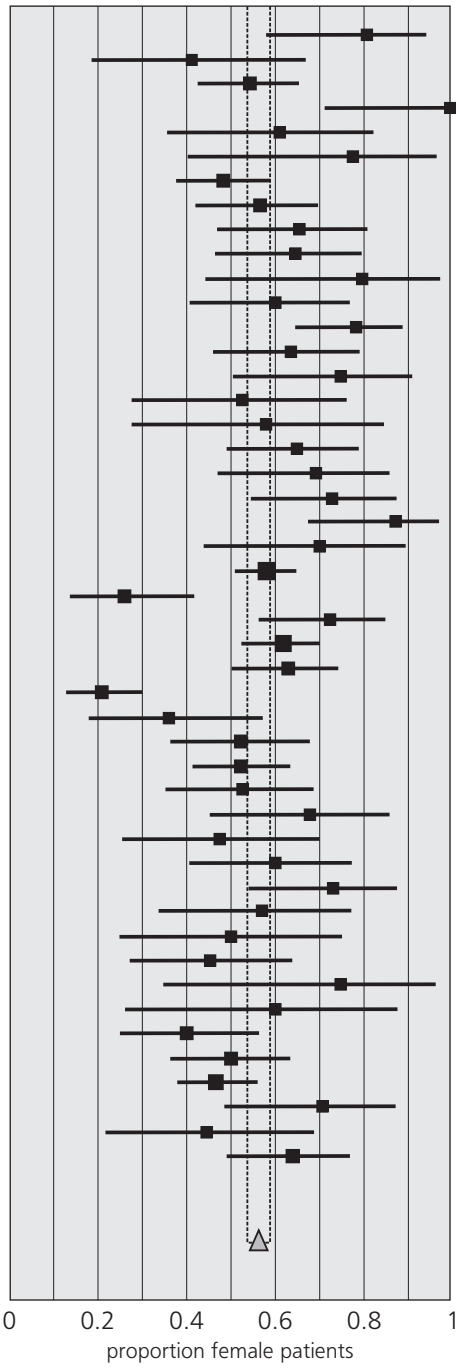
| Included study of CSX patients | year | n | Female (%) | Mean age (Y) |
|---|---|---|---|---|
| Lee [41] | 2008 | 21 | 81 | 55 |
| Timurkaynak [61] | 2008 | 79 | 54 | 50 |
| Cemin [11] | 2008 | 11 | 100 | 59 |
| Zorc-Pleskovic [66] | 2008 | 31 | 100 | 55 |
| Lanza [38] | 2008 | 18 | 61 | 58 |
| Altun [2] | 2007 | 9 | 77 | 49 |
| Cotrim [12] | 2008 | 91 | 48 | 51 |
| Asbury [5] | 2008 | 64 | 100 | 58 |
| Demir [18] | 2008 | 17 | 41 | 57 |
| Grabczewska [23] | 2007 | 53 | 57 | 55 |
| Li [44] | 2007 | 36 | 100 | NA |
| Okyay [48] | 2007 | 32 | 66 | 53 |
| Dabek [15] | 2007 | 34 | 65 | 57 |
| Yildiz [64] | 2007 | 10 | 79 | 49 |
| Kayikcioglu [33] | 2007 | 30 | 60 | 46 |
| Mao [45] | 2007 | 51 | 78 | 21 |
| Dabek [14] | 2007 | 36 | 65 | 57 |
| Vermeltfoort [63] | 2007 | 20 | 75 | 55 |
| Galiuto [21] | 2007 | 17 | 53 | 55 |
| Alroy [1] | 2007 | 42 | 100 | 52 |
| Huang [29] | 2007 | 12 | 60 | 63 |
| Guzik [28] | 2007 | 43 | 65 | 44 |
| Gur [26] | 2007 | 23 | 70 | 49 |
| Gur [27] | 2007 | 23 | NA | NA |
| Sgueglia [59] | 2007 | 30 | 73 | 61 |
| Russell [55] | 2007 | 24 | 89 | 54 |
| Sen [56] | 2007 | 203 | 58 | 53 |
| Shmilovich [60] | 2007 | 17 | 71 | 58 |

**TABLE 3:** *Cont.*

| Included study of CSX patients | year | n | Female (%) | Mean age (Y) |
|---|---|---|---|---|
| de Vries [17] | 2006 | 42 | 26 | 58 |
| Nam [47] | 2006 | 52 | NA | NA |
| Eskandarian [19] | 2006 | 40 | 73 | 46 |
| Cay [10] | 2006 | 126 | 62 | 53 |
| Jadhav [30] | 2006 | 52 | 100 | 56 |
| Czepczynski [13] | 2006 | 68 | 63 | 45 |
| Leu [43] | 2006 | 92 | 21 | 64 |
| Lanza [40] | 2005 | 10 | 59 | 70 |
| Cay [9] | 2005 | 80 | 52 | 51 |
| On [49] | 2005 | 36 | 53 | 36 |
| Guo [25] | 2005 | 22 | 68 | 48 |
| Masci [46] | 2005 | 41 | NA | 53 |
| Senen [57] | 2005 | 21 | 48 | 56 |
| Pasqui [51] | 2005 | 30 | 60 | 54 |
| Sestito [58] | 2005 | 30 | 73 | 60 |
| De Candia [16] | 2005 | 21 | 57 | 55 |
| Valeriani [62] | 2005 | 16 | 50 | 60 |
| Cavusoglu [8] | 2005 | 31 | 45 | 52 |
| Kolasinska-Kloch [36] | 2004 | 42 | 52 | 46 |
| Kolasilska-Kloch [35] | 2004 | 25 | 36 | 49 |
| Altun [3] | 2004 | 8 | 75 | 46 |
| Asbury [4] | 2004 | 100 | 100 | 61 |
| Fabian [20] | 2004 | 40 | 40 | 55 |
| Lanza [39] | 2004 | 55 | 50 | 57 |
| Qian [54] | 2004 | 126 | 47 | 53 |
| Osamichi [50] | 2004 | 24 | 71 | 58 |
| Gorgulu [22] | 2003 | 18 | 44 | 51 |
| Pizzi [53] | 2004 | NA | NA | 59 |
| Kidawa [34] | 2003 | 50 | 64 | 49 |

NA= not available

The proportion of women in the 47 studies of CSX patients varied considerably ranging from 0.21 to 1.0, with a pooled estimate of 0.56 (95% confidence interval: 0.54-0.59), see also figure 1. Hence, there is a significantly higher proportion of woman compared to males in the group of patients with CSX.




| first author & year: | proportion | (95% CI) |
|---|---|---|
| Lee 2008 | 0.81 | 0.58 - 0.95 |
| Demir 2008 | 0.41 | 0.18 - 0.67 |
| Timurkaynak 2008 | 0.54 | 0.43 - 0.66 |
| Cemin 2008 | 1.00 | 0.72 - 1.00 |
| Lanza 2008 | 0.61 | 0.36 - 0.83 |
| Altun 2008 | 0.78 | 0.40 - 0.97 |
| Cotrim 2008 | 0.48 | 0.38 - 0.59 |
| Grabczewska 2007 | 0.57 | 0.42 - 0.70 |
| Okyay 2007 | 0.66 | 0.47 - 0.81 |
| Dabek 2007 | 0.65 | 0.46 - 0.80 |
| Yildiz 2007 | 0.80 | 0.44 - 0.97 |
| Kayikcioglu 2007 | 0.60 | 0.41 - 0.77 |
| Mao 2007 | 0.78 | 0.65 - 0.89 |
| Dabek 2007 | 0.64 | 0.46 - 0.79 |
| Vermeltfoort 2007 | 0.75 | 0.51 - 0.91 |
| Galiuto 2007 | 0.53 | 0.28 - 0.77 |
| Huang 2007 | 0.58 | 0.28 - 0.85 |
| Guzik 2007 | 0.65 | 0.49 - 0.79 |
| Guzik 2007 | 0.70 | 0.47 - 0.87 |
| Sgueglia 2007 | 0.73 | 0.54 - 0.88 |
| Russell 2007 | 0.88 | 0.68 - 0.97 |
| Shmilovich 2006 | 0.71 | 0.44 - 0.90 |
| Sen 2007 | 0.58 | 0.51 - 0.65 |
| de Vries 2006 | 0.26 | 0.14 - 0.42 |
| Eskandarian 2006 | 0.73 | 0.56 - 0.85 |
| Cay 2006 | 0.62 | 0.53 - 0.70 |
| Czepczynski 2006 | 0.63 | 0.51 - 0.75 |
| Leu2006 | 0.21 | 0.13 - 0.30 |
| Kolasilska - Kloch 2004 | 0.36 | 0.18 - 0.57 |
| Kolasilska - Kloch 2004 | 0.52 | 0.36 - 0.68 |
| Cay 2005 | 0.53 | 0.41 - 0.64 |
| On 2005 | 0.53 | 0.35 - 0.70 |
| Guo 2005 | 0.68 | 0.45 - 0.86 |
| Senen 2005 | 0.48 | 0.26 - 0.70 |
| Pasqui 2005 | 0.60 | 0.41 - 0.77 |
| Sestito 2005 | 0.73 | 0.54 - 0.88 |
| De Candia 2005 | 0.57 | 0.34 - 0.78 |
| Valeriani 2005 | 0.50 | 0.25 - 0.75 |
| Cavusoglu 2005 | 0.45 | 0.27 - 0.64 |
| Altun 2004 | 0.75 | 0.35 - 0.97 |
| Lanza 2005 | 0.60 | 0.26 - 0.88 |
| Fabian 2004 | 0.40 | 0.25 - 0.57 |
| Lanza 2004 | 0.50 | 0.36 - 0.64 |
| Qian 2004 | 0.47 | 0.38 - 0.56 |
| Osamichi 2004 | 0.71 | 0.49 - 0.87 |
| Gorgulu 2003 | 0.44 | 0.22 - 0.69 |
| Kidawa 2003 | 0.64 | 0.49 - 0.77 |
| pooled proportion : | 0.56 | (0.54 to 0.59) |

**FIGURE 1:** plot of proportion of women of individual studies, including 95% confidence intervals

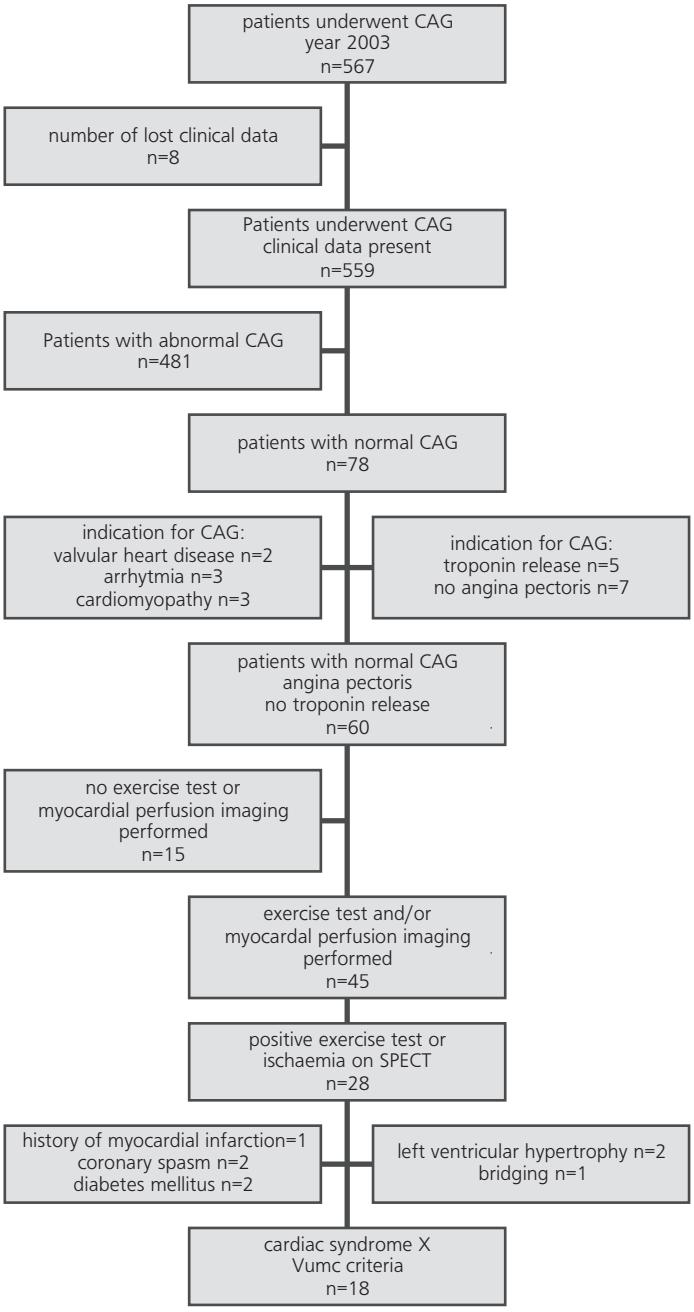



**FIGURE 2:** flowchart

## CSX incidence

567 CAGs were performed in one year at a general hospital. Figure 2 is a flowchart showing how we analyzed the available information.

The main stages are:

- Original CAGs or clinical data could not be found for 8 patients, leaving 559 cases for analysis.
- 78 (14%) of the available 559 CAGs were considered as absolutely normal.
- Excluding 13 cases with no angina pectoris as indication for CAG, and another 5 with an acute coronary syndrome, resulted in an incidence of 60 (11%) CSX patients according to the broad diagnosis of CSX (angina pectoris and normal coronary arteries). (1, 2, 19, 35, 59)
- Another 15 cases were excluded owing to the lack of exercise stress tests or myocardial perfusion imaging preceding the CAG.
- Of the remaining 45 cases, 28 were *included* owing to positive results for ischaemia from exercise tests or SPECT.
- Finally, a much stricter definition of CSX was obtained by using the main exclusion criteria shown in the second-to-last stage in figure 2. This strict definition resulted in an attributable CSX incidence of 18 (3%) patients.

# DISCUSSION

## CSX definitions and incidences

The present review of recent archival literature demonstrates that there is a wide range of definitions of CSX. This wide range of definitions has large effects on the attributable incidence of CSX, as has been shown by an analysis of all available CAGs and other clinical data for a population of patients treated in one year at a general hospital.

Generally it is stated that patients with chest pain and normal coronary arteriogram may represent as many as 10 to 20 % of those undergoing coronary arteriography because of clinical suspicion of angina. (1) This is in broad agreement with our analysis result that 11% of patients had a normal CAG. The rather low incidence of normal CAG can be the result of the use of rather strict criteria for a normal CAG including a consensus reading by two independent readers of the CAG's.

It is generally accepted (e.g. in important textbooks) that the majority of the CSX patients are women. (1, 63) Some authors have suggested that CSX is a women's disease, however, we found in this review of a pooled relative female frequency of 56% in a population of more than 1900 CSX patients. Hence, our data do not support the assumption that CSX is a women's disease since 44% is of male gender. Potential pathofysiological explanations, such as estrogen depletion, which are based upon the female gender apply only for a part of the CSX patients. (64)

## Inclusion and exclusion criteria

The literature survey showed that the inclusion and exclusion criteria varied. This was especially the case for the exclusion criteria.



The definition of 'normal coronary arteries' was particularly unclear. Most studies did not define a normal CAG, and some included patients with coronary artery disease (CAD) ranging from minimal to stenoses up to 50% of luminal diameter. Obviously, normal coronary arteries are the cornerstone of the diagnosis of CSX. Hence, there should be no doubt regarding the use of this inclusion criterion for studies of CSX patients. Future studies of CSX patients should make a clear description regarding the evaluation and results of the CAG studies of the coronary artery anatomy.

The so-called broad diagnosis for CSX, a combination of 2 inclusion criteria (angina pectoris and normal coronary arteries) was used in only 4 studies (7%).

Most studies used a combination of 3 inclusion criteria, namely (effort induced) angina pectoris, positive exercise test result and a normal CAG, as an inclusion criterion. This definition was used in 46 of 57 studies (81%). The use of this additional inclusion criterion resulted in a decrease of the incidence of CSX to 7 % in our population. The definition of a positive exercise stress test appears to be more standardized than the definition of a normal CAG. Most publications used a ST depression ≥1 mm as a positive exercise stress test, in only 12 of the 57 studies the definition of a positive stress test was not specified.

The use of specific exclusion criteria ranged from 2 to 58% of the selected studies of CSX patients, often depending on the main objectives of the studies, for example the use of thrombocytopenia as an exclusion criterion in a study investigating the mean platelet volume. (43)

The most frequently mentioned exclusion criteria are valvular heart disease, diabetes mellitus, left ventricular hypertrophy, hypertension and cardiomyopathy. Microvascular dysfunction has been assessed in patients with diabetes mellitus and hypertension with normal CAG. Interestingly coronary flow reserve may be reversible in patients after anti-hypertensive therapy for instance. (65) However, regarding CSX definition in most international studies diabetes mellitus and hypertension are considered as exclusion criteria.

The existence of such a long list of exclusion criteria in the selection process of CSX patients illustrates the lack of agreement between the different research groups regarding the origins of this syndrome. Beside the use of a standard and fixed combination of inclusion criteria future studies should apply a standard combination of exclusion criteria.

In a recent editorial Camici proposed following exclusion criteria in order to obtain a more homogeneous set of cardiac syndrome X patients: absence of left bundle branch block; absence of even minimal irregularities on the angiogram; no evidence of diabetes

mellitus, arterial hypertension, hyperlipidaemia, valve disease, epicardial arterial spasm, and cardiomyopathy. (66)

In our selection of CSX patients we decided to include only patients with completely normal coronary angiograms, effort-induced angina pectoris, positive exercise stress test and/or positive SPECT study. Furthermore, we decided to add arrhythmias, left ventricular hypertrophy, myocardial infarction in the medical history and myocardial bridging to the exclusion criteria proposed by Camici. These inclusion and exclusion criteria resulted in an attributable CSX incidence of only 3 %.

# CONCLUSION

The wide range of definitions of CSX in recent literature and the variations in inclusion and exclusion criteria, particularly the latter, make interpretation of the results of individual studies difficult. This shows the need for a generally accepted definition of CSX.

# ACKNOWLEDGEMENTS

We thank Dr R.J.H. Wanhill for his critical review and editing of the manuscript
**Conflict of interest:** none declared

## Reference List


1. Zipes DP, Libby P, Bonow RO, Braunwald E. *Braunwald's heart disease: A textbook of cardiovascular medicine*. 8 ed. Philadelphia: Saunders-Elsevier; 2008.
2. Zorc-Pleskovic R, Vraspir-Porenta O, Zorc M, Milutinovic A, Petrovic D. Inflammatory changes in small blood vessels in the endomyocardium of cardiac syndrome X in female patients with increased C-reactive protein. *Folia Biol (Praha)* 2008;54(1):30-32.
3. Lanza GA. Cardiac syndrome X: a critical overview and future perspectives. *Heart* 2007 Feb;93(2):159-166.
4. Grawe H, Katoh M, Kuhl HP. Stress cardiomyopathy mimicking acute coronary syndrome: case presentation and review of the literature. *Clin Res Cardiol* 2006 Mar;95(3):179-185.
5. Athanasiadis A, Vogelsberg H, Hauer B, Meinhardt G, Hill S, Sechtem U. Transient left ventricular dysfunction with apical ballooning (tako-tsubo cardiomyopathy) in Germany. *Clin Res Cardiol* 2006 Jun;95(6):321-328.
6. Leichman JG, Lavis VR, Aguilar D, Wilson CR, Taegtmeyer H. The metabolic syndrome and the heart–a considered opinion. *Clin Res Cardiol* 2006 Jan;95 Suppl 1:i134-i141.
7. Demir H, Kahraman G, Isgoren S, Tan YZ, Kilic T, Berk F. Evaluation of post-stress left ventricular dysfunction and its relationship with perfusion abnormalities using gated SPECT in patients with cardiac syndrome X. *Nucl Med Commun* 2008 Mar;29(3):208-214.
8. Gorgulu S, Uslu N, Eren M, Celik S, Yildirim A, Dagdeviren B, et al. Aortic stiffness in patients with cardiac syndrome X. *Acta Cardiol* 2003 Dec;58(6):507-511.
9. Sen N, Tavil Y, Yazici HU, Abacl A, Cengel A. Coronary blood flow in patients with cardiac syndrome X. *Coron Artery Dis* 2007 Feb;18(1):45-48.
10. Alroy S, Preis M, Barzilai M, Cassel A, Lavie L, Halon DA, et al. Endothelial cell dysfunction in women with cardiac syndrome X and MTHFR C677T mutation. *Isr Med Assoc J* 2007 Apr;9(4):321-325.
11. Dabek J, Wilczok T, Gasior Z, Kucia-Kuzma S, Twardowski R, Kulach A. Gene expression of kinin receptors B1 and B2 in PBMC from patients with cardiac syndrome X. *Scand Cardiovasc J* 2007 Dec;41(6):391-396.
12. Lee BK, Durairaj A, Mehra A, Wenby RB, Meiselman HJ, Alexy T. Microcirculatory dysfunction in cardiac syndrome X: role of abnormal blood rheology. *Microcirculation* 2008 Jul;15(5):451-459.
13. Timurkaynak T, Balcioglu S, Arslan U, Kocaman SA, Cengel A. Plasma homocysteine level in cardiac syndrome X and its relation with duke treadmill score. *Saudi Med J* 2008 Mar;29(3):364-367.
14. Cemin R, Erlicher A, Fattor B, Pitscheider W, Cevese A. Reduced coronary flow reserve and parasympathetic dysfunction in patients with cardiovascular syndrome X. *Coron Artery Dis* 2008 Feb;19(1):1-7.
15. Lanza GA, Buffon A, Sestito A, Natale L, Sgueglia GA, Galiuto L, et al. Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. *J Am Coll Cardiol* 2008 Jan 29;51(4):466-472.
16. Altun A, Turgut N, Tatli E, Ugur-Altun B, Balci K. Sympathetic skin response and RR interval variation in patients with cardiac syndrome X. *Angiology* 2007 Dec 20;58(6):747-750.
17. Cotrim C, Almeida AG, Carrageta M. Exercise-induced intra-ventricular gradients as a frequent potential cause of myocardial ischemia in cardiac syndrome X patients. *Cardiovasc Ultrasound* 2008;6:3.

18. Asbury EA, Slattery C, Grant A, Evans L, Barbir M, Collins P. Cardiac rehabilitation for the treatment of women with chest pain and normal coronary arteries. *Menopause* 2008 May;15(3):454-460.

19. Grabczewska Z, Thews M, Goralczyk K, Kubica J. Endothelial function in patients with chest pain and normal coronary angiograms. *Kardiol Pol* 2007 Oct;65(10):1199-1206.

20. Li JJ, Zhu CG, Nan JL, Li J, Li ZC, Zeng HS, et al. Elevated circulating inflammatory markers in female patients with cardiac syndrome X. *Cytokine* 2007 Dec;40(3):172-176.

21. Okyay K, Cengel A, Sahinarslan A, Tavil Y, Turkoglu S, Biberoglu G, et al. Plasma asymmetric dimethylarginine and L-arginine levels in patients with cardiac syndrome X. *Coron Artery Dis* 2007 Nov;18(7):539-544.

22. Yildiz M, Altun A, Ozbay G. Assessment of arterial distensibility in patients with cardiac syndrome X. *Angiology* 2007 Aug;58(4):458-462.

23. Kayikcioglu M, Saygi S, Azarsiz E, Can LH, Kultursay H, Sozmen EY. Serum paraoxonase 1 activity and oxidative markers of LDL in patients with cardiac syndrome X. *Acta Cardiol* 2007 Jun;62(3):245-249.

24. Mao JY, Ge YB, Wang HH, Wang Q, Zhang Y, Yu DL, et al. Summary of 32 patients with cardiac syndrome X treated by TCM therapy of regulating qi relieving chest stuffiness and promoting blood circulation. *Chin J Integr Med* 2007 Mar;13(1):17-21.

25. Dabek J, Kulach A, Wilczok T, Mazurek U, Jakubowski D, Gasior Z. Transcriptional activity of genes encoding interferon gamma (IFNgamma) and its receptor assessed in peripheral blood mononuclear cells in patients with cardiac syndrome X. *Inflammation* 2007 Aug;30(3-4):125-129.

26. Vermeltfoort IA, Bondarenko O, Raijmakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, et al. Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study. *Eur Heart J* 2007 Jul;28(13):1554-1558.

27. Galiuto L, Sestito A, Barchetta S, Sgueglia GA, Infusino F, La Rosa C, et al. Noninvasive evaluation of flow reserve in the left anterior descending coronary artery in patients with cardiac syndrome X. *Am J Cardiol* 2007 May 15;99(10):1378-1383.

28. Huang PH, Chen YH, Chen YL, Wu TC, Chen JW, Lin SJ. Vascular endothelial function and circulating endothelial progenitor cells in patients with cardiac syndrome X. *Heart* 2007 Sep;93(9):1064-1070.

29. Guzik P, Rogacka D, Trachalski J, Minczykowski A, Balinski M, Wykretowicz A, et al. Comparison of the exercise treadmill test and 24-hour ECG Holter monitoring in patients with syndrome X or coronary atherosclerosis. *Kardiol Pol* 2007 Mar;65(3):262-269.

30. Gur M, Yildiz A, Demirbag R, Yilmaz R, Aslan M, Ozdogru I, et al. Paraoxonase and arylesterase activities in patients with cardiac syndrome X, and their relationship with oxidative stress markers. *Coron Artery Dis* 2007 Mar;18(2):89-95.

31. Gur M, Yildiz A, Demirbag R, Yilmaz R, Kocyigit A, Celik H, et al. Increased lymphocyte deoxyribonucleic acid damage in patients with cardiac syndrome X. *Mutat Res* 2007 Apr 1;617(1-2):8-15.

32. Sgueglia GA, Sestito A, Spinelli A, Cioni B, Infusino F, Papacci F, et al. Long-term follow-up of patients with cardiac syndrome X treated by spinal cord stimulation. *Heart* 2007 May;93(5):591-597.

33. Russell SJ, Di Stefano EM, Naffati MT, Brown O, Saltissi S. The effects of the angiotensin II receptor (type I) antagonist irbesartan in patients with cardiac syndrome X. *Heart* 2007 Feb;93(2):253-254.

34. Shmilovich H, Deutsch V, Roth A, Miller H, Keren G, George J. Circulating endothelial progenitor cells in patients with cardiac syndrome X. *Heart* 2007 Sep;93(9):1071-1076.

35. de Vries J, DeJongste MJ, Jessurun GA, Jager PL, Staal MJ, Slart RH. Myocardial perfusion quantification in patients suspected of cardiac syndrome X with positive and negative exercise testing: a [13N]ammonia positron emission tomography study. *Nucl Med Commun* 2006 Oct;27(10):791-794.

36. Nam CW, Kim KS, Lee YS, Lee SH, Han SW, Hur SH, et al. The incidence of gastro-esophageal disease for the patients with typical chest pain and a normal coronary angiogram. *Korean J Intern Med* 2006 Jun;21(2):94-96.

37. Eskandarian R, Malek M, Mousavi SH, Babaei M. Association of Helicobacter pylori infection with cardiac syndrome X. *Singapore Med J* 2006 Aug;47(8):704-706.

38. Cay S, Guray U, Korkmaz S. Increased aortic pulse and fractional pulse pressures in patients with cardiac syndrome X. *Blood Press* 2006;15(3):179-184.

39. Jadhav ST, Ferrell WR, Petrie JR, Scherbakova O, Greer IA, Cobbe SM, et al. Microvascular function, metabolic syndrome, and novel risk factor status in women with cardiac syndrome X. *Am J Cardiol* 2006 Jun 15;97(12):1727-1731.

40. Czepczynski R, Smolarek I, Rogacka D, Kazmierczak M, Wysocki H, Sowinski J. Myocardial perfusion SPECT with dipyridamole stress test in cardiac syndrome X. *Nuklearmedizin* 2006;45(3):111-114.

41. Leu HB, Lin CP, Lin WT, Wu TC, Lin SJ, Chen JW. Circulating mononuclear superoxide production and inflammatory markers for long-term prognosis in patients with cardiac syndrome X. *Free Radic Biol Med* 2006 Mar 15;40(6):983-991.

42. Lanza GA, Sestito A, Sgueglia GA, Infusino F, Papacci F, Visocchi M, et al. Effect of spinal cord stimulation on spontaneous and stress-induced angina and 'ischemia-like' ST-segment depression in patients with cardiac syndrome X. *Eur Heart J* 2005 May;26(10):983-989.

43. Cay S, Biyikoglu F, Cihan G, Korkmaz S. Mean platelet volume in the patients with cardiac syndrome X. *J Thromb Thrombolysis* 2005 Dec;20(3):175-178.

44. On YK, Park R, Hyon MS, Kim SK, Kwon YJ. Are low total serum antioxidant status and elevated levels of C-reactive protein and monocyte chemotactic protein-1 associated with cardiac syndrome X? *Circ J* 2005 Oct;69(10):1212-1217.

45. Guo H, Lee JD, Guo M, Lu Y, Tang F, Ueda T. Status of intracellular and extracellular magnesium concentration in patients with cardiac syndrome X. *Acta Cardiol* 2005 Jun;60(3):259-263.

46. Masci PG, Laclaustra M, Lara JG, Kaski JC. Brachial artery flow-mediated dilation and myocardial perfusion in patients with cardiac syndrome X. *Am J Cardiol* 2005 Jun 15;95(12):1478-1480.

47. Senen K, Ileri M, Alper A, Yetkin F, Atak R, Hisar I, et al. Increased levels of soluble adhesion molecules E-selectin and P-selectin in patients with cardiac syndrome X. *Angiology* 2005 May;56(3):273-277.

48. Pasqui AL, Puccetti L, Di Renzo M, Bruni F, Camarri A, Palazzuoli A, et al. Structural and functional abnormality of systemic microvessels in cardiac syndrome X. *Nutr Metab Cardiovasc Dis* 2005 Feb;15(1):56-64.

49. Sestito A, Maccallini A, Sgueglia GA, Infusino F, Larosa C, Aurigemma C, et al. Platelet reactivity in response to mental stress in syndrome X and in stable or unstable coronary artery disease. *Thromb Res* 2005;116(1):25-31.

50. De Candia E, Lanza GA, Romagnoli E, Ciabattoni G, Sestito A, Pasqualetti P, et al. Abnormal pH-sensing of platelet Na+/H+ exchanger in patients with cardiac syndrome X. *Int J Cardiol* 2005 Apr 28;100(3):371-376.

51. Valeriani M, Sestito A, Le Pera D, De Armas L, Infusino F, Maiese T, et al. Abnormal cortical pain processing in patients with cardiac syndrome X. *Eur Heart J* 2005 May;26(10):975-982.

52. Cavusoglu Y, Entok E, Timuralp B, Vardareli E, Kudaiberdieva G, Birdane A, et al. Regional distribution and extent of perfusion abnormalities, and the lung to heart uptake ratios during exercise thallium-201 SPECT imaging in patients with cardiac syndrome X. *Can J Cardiol* 2005 Jan;21(1):57-62.

53. Kolasinska-Kloch W, Furgala A, Krolczyk G, Kloch M, Szumanska M, Laskiewicz J, et al. Cardiac syndrome X–autonomic system disorders. *Folia Med Cracov* 2004;45(3-4):19-29.

54. Kolasilska-Kloch W, Lesniak W, Leszczynska-Golabek I, Kiec-Wilk B, Kloch M. Exercise tolerance and hyperinsulinemia in cardiac syndrome X. *Folia Med Cracov* 2004;45(1-2):13-23.

55. Altun A, Ugur-Altun B, Tatli E. Decreased serum osteoprotegerin levels in patients with cardiac syndrome X. *J Endocrinol Invest* 2004 Oct;27(9):839-843.

56. Asbury EA, Creed F, Collins P. Distinct psychosocial differences between women with coronary heart disease and cardiac syndrome X. *Eur Heart J* 2004 Oct;25(19):1695-1701.

57. Fabian E, Varga A, Picano E, Vajo Z, Ronaszeki A, Csanady M. Effect of simvastatin on endothelial function in cardiac syndrome X patients. *Am J Cardiol* 2004 Sep 1;94(5):652-655.

58. Lanza GA, Sestito A, Cammarota G, Grillo RL, Vecile E, Cianci R, et al. Assessment of systemic inflammation and infective pathogen burden in patients with cardiac syndrome X. *Am J Cardiol* 2004 Jul 1;94(1):40-44.

59. Qian JY, Ge JB, Fan B, Wang QB, Chen HZ, Baumgart D, et al. Identification of syndrome X using intravascular ultrasound imaging and Doppler flow mapping. *Chin Med J (Engl )* 2004 Apr;117(4):521-527.

60. Osamichi S, Kouji K, Yoshimaro I, Tadashi U, Hiroichi T, Seiyu K, et al. Myocardial glucose metabolism assessed by positron emission tomography and the histopathologic findings of microvessels in syndrome X. *Circ J* 2004 Mar;68(3):220-226.

61. Pizzi C, Manfrini O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac Syndrome X: role of superoxide dismutase activity. *Circulation* 2004 Jan 6;109(1):53-58.

62. Kidawa M, Krzeminska-Pakula M, Peruga JZ, Kasprzak JD, Trzos E. Cardiological syndrome X. Non-invasive assessment of endothelial function and arterial compliance. *Kardiol Pol* 2003 Nov;59(11):385-396.

63. Kaski JC. Overview of gender aspects of cardiac syndrome X. *Cardiovasc Res* 2002 Feb 15;53(3):620-626.

64. Kaski JC. Cardiac syndrome X in women: the role of oestrogen deficiency. *Heart* 2006 May;92 Suppl 3:iii5-iii9.

65. Petkow Dimitrow P, Krzanowski M, Nizankowski R, Szczeklik A, Dubiel JS. Effect of verapamil on systolic and diastolic coronary blood flow velocity in asymptomatic and mildly symptomatic patients with hypertrophic cardiomyopathy. *Heart* 2000 Mar;83(3):262-266.

66. Camici PG. Is the chest pain in cardiac syndrome X due to subendocardial ischaemia? *Eur Heart J* 2007 Jul;28(13):1539-1540.

# Chapter 3

Acta Cardiologica 2009 Jun; 64(3):415-417

Case report

# Improved myocardial perfusion preceding clinical response on bosentan treatment for coronary vasospasm

Ilse A.C. Vermeltfoort[a] MD, Pieter G.H.M. Raijmakers[a] MD,PhD, and Pieter W. Kamphuisen[b] MD,PhD

a. Department of Nuclear Medicine & PET Research, VU University Medical Centre, Amsterdam, The Netherlands

b. Department of Vascular Medicine, Academic Medical Centre, Amsterdam, The Netherlands

# SUMMARY

Many patients suffer from persistent angina due to coronary vasospasm despite optimal medical treatment.

We treated a 46-year-old patient with severe and treatment resistant coronary vasospasm with the endothelin-receptor antagonist bosentan. Using oxygen-15-labeled water in conjunction with oxygen 15-labeled carbon monoxide Positron Emission Tomography, we measured an impaired coronary flow reserve (CFR) in 6 out of 13 segments directly before the start of bosentan therapy. A repeated PET measurement after 16 weeks of bosentan treatment revealed a completely normalized CFR in this patient. Furthermore, the patient reported less frequent and less severe chest pain. Our data suggest a potential role of endothelin-receptor antagonists for patients with severe coronary vasospasms.

In 2001 a 46-year old man suffered from a myocardial infarction caused by a significant stenosis of the left coronary artery, for which a bare metal stent was placed, and the patient was further treated with aspirin, a beta blocker, an ACE-inhibitor, and statins. His medical history further mentioned hypertension and hypercholesterolemia. Owing to persistent angina, in 2003 a coronary angiography was performed that showed no significant stenoses of the coronary arteries. Provocation with intracoronary acetylcholine-injection induced severe multivessel proximal and distal coronary vasospasm and chest pain. A diagnosis of coronary vasospasm was made and the patient was additionally treated with long-acting calcium antagonists and nitrate. Despite this medication, daily severe complaints of angina persisted. Since treatment with calcium antagonist and nitrate was at maximal dosage and daily severe chest pain persisted, we started additional treatment with bosentan (Tracleer®, Actelion Pharmaceuticals, Switzerland) according to the protocol used in patients with pulmonary hypertension. An oral dose of 62,5 mg b.i.d. was given for one month, followed by three months of 125 mg b.i.d. After six weeks, complaints significantly decreased: chest pain was clearly less severe and the attacks occurred less often. Side effects of bosentan consisted of nasopharyngitis, hypotension, and flushing.

A PET study using the tracer $H_2{}^{15}O$ in conjunction of $C^{15}O$ showed before the start of bosentan therapy an abnormal coronary flow reserve (CFR<2.0) in 6 out of 13 segments explaining the patient's severe chest pain. The mean rest myocardial blood flow value was 0.9 ± 0.3 mL/min/mL myocardial tissue. The mean stress myocardial blood flow value was 1.8 ± 1.2 mL/min/mL myocardial tissue (see figure 1). The mean coronary flow reserve was 2.0 ± 1.4.

After 16 weeks of bosentan therapy the study was repeated. The coronary flow reserve quantitatively measured by PET was totally normal in all segments. The mean rest myocardial blood flow value was 1.3 ± 0.4 mL/min/mL myocardial tissue. The mean stress myocardial blood flow value was 6.5 ± 3.0 mL/min/mL myocardial tissue (see figure 1). The mean coronary flow reserve after bosentan therapy was 4.9 ± 3.5.

This case report is the first to show a beneficial effect of treatment with the endothelin-receptor antagonist bosentan in a patient with severe, treatment-resistant, vasospastic angina. After 16 weeks of bosentan therapy the clinical complaints of angina greatly decreased and the coronary flow reserve was completely normalized.

In 1959 Prinzmetal and colleagues described an unusual syndrome of cardiac pain secondary to myocardial ischaemia. This pain occurred almost exclusively at rest and was associated with ST segment elevations on the ECG. The original hypothesis of Prinzmetal and colleagues, that variant angina is the result of transient increases in coronary vasomotor tone or vasospasm, has been convincingly demonstrated by coronary angiography. The coronary spasm can be induced by intracoronary acetylcholine (Ach), which causes vasodilatation when the endothelium is functioning normally. The spasm

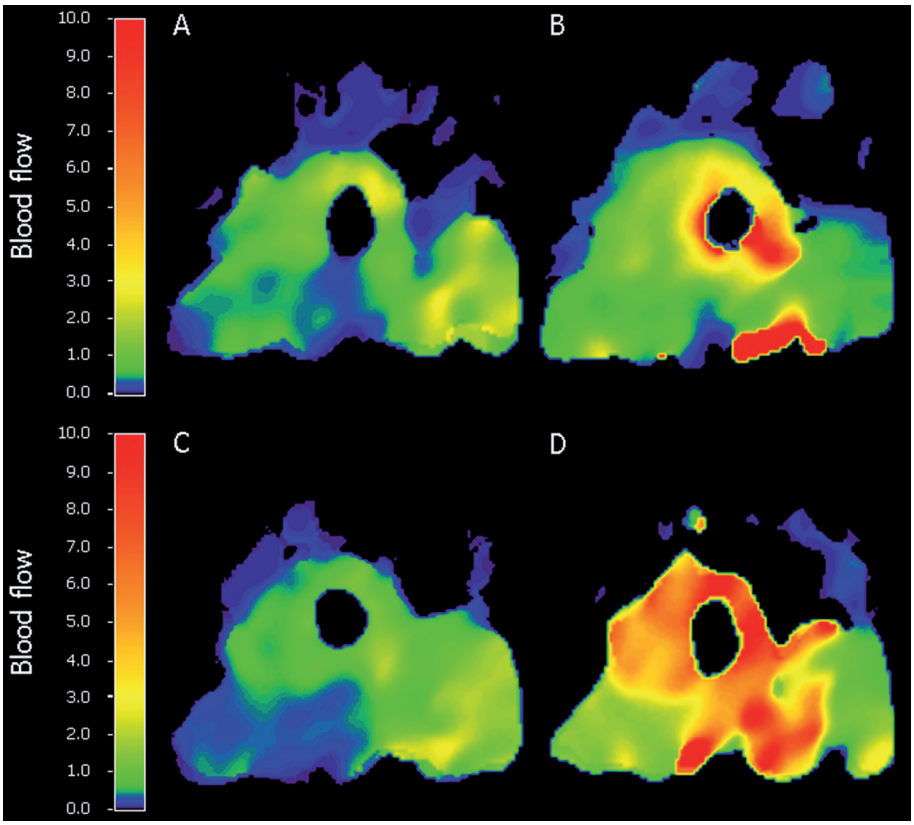



**FIGURE 1:** Short-axis images indicating absolute myocardial blood before bosentan at rest (A) and during stress (B). Panel C and D show myocardial blood flow after bosentan at rest (C) and during stress (D)

is promptly relieved by nitroglycerin, which causes vasodilation through its direct action on the smooth muscle. This phenomenon suggests the possibility that patients with coronary spasm have a disturbance in the endothelial function of their coronary arteries (1-3). Endothelial dysfunction appears to be mediated by endothelin (2,4-6). Endothelin has two known receptor subtypes, $ET_A$ and $ET_B$. $ET_A$ is located predominately on vascular smooth muscle cells (VSMC) and induces a vasoconstrictor effect, while $ET_B$ is located on endothelial cells and VSMC, and has both a vasoconstrictor and vasodilator effect.

Bosentan is the first endothelin-receptor antagonist with an affinity for both $ET_A$ and $ET_B$. Bosentan is an effective treatment for primary pulmonary hypertension (7). Recently, Allanore et al. reported the increase of myocardial perfusion using magnetic resonance imaging after bosentan treatment in patients with systemic sclerosis, a disease associated with an abnormal vasoreactivity in the microcirculation (8).

Medical treatment for vasospastic angina includes (besides risk factor modification) a calcium antagonist on its own or in combination with long acting nitrates. Other therapeutic options like prazosin, a selective alpha adrenoreceptor blocker, oestradiol supplementation and endoscopic thoracic symphatectomy have also been reported to be of value (9-11).

As we have shown, endothelin receptor antagonists like bosentan may be effective in patients with severe coronary spasms, especially when other treatment fails. However, more studies are needed to assess the exact therapeutic value of these agents.Although this is a preliminary observation, our data suggest a potential role of bosentan for patients with severe therapy-resistant coronary vasospasms.

**Disclosures**: none

# ACKNOWLEDGEMENTS

We thank Dr J.M. Lubberink and R. Kloet for preparing the figures and Dr R.J.H. Wanhill for his critical review of the manuscript.

## Reference List




1. Kawano H, Motoyama T, Yasue H, Hirai N, Waly HM, Kugiyama K, et al. Endothelial function fluctuates with diurnal variation in the frequency of ischemic episodes in patients with variant angina. *J Am Coll Cardiol* 2002 Jul 17;40(2):266-270.
2. Kaski JC, Crea F, Meran D, Rodriguez L, Araujo L, Chierchia S, et al. Local coronary supersensitivity to diverse vasoconstrictive stimuli in patients with variant angina. *Circulation* 1986 Dec;74(6):1255-1265.
3. Yasue H, Kugiyama K. Coronary spasm: clinical features and pathogenesis. *Intern Med* 1997 Nov;36(11):760-765.
4. Berger R, Stanek B, Hulsmann M, Frey B, Heher S, Pacher R, et al. Effects of endothelin a receptor blockade on endothelial function in patients with chronic heart failure. *Circulation* 2001 Feb 20;103(7):981-986.
5. Cardillo C, Campia U, Kilcoyne CM, Bryant MB, Panza JA. Improved endothelium-dependent vasodilation after blockade of endothelin receptors in patients with essential hypertension. *Circulation* 2002 Jan 29;105(4):452-456.
6. Spieker LE, Hurlimann D, Ruschitzka F, Corti R, Enseleit F, Shaw S, et al. Mental stress induces prolonged endothelial dysfunction via endothelin-A receptors. *Circulation* 2002 Jun 18;105(24):2817-2820.
7. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002 Mar 21;346(12):896-903.
8. Allanore Y, Meune C, Vignaux O, Weber S, Legmann P, Kahan A. Bosentan increases myocardial perfusion and function in systemic sclerosis: a magnetic resonance imaging and Tissue-Doppler echography study. *J Rheumatol* 2006 Dec;33(12):2464-2469.
9. Kawano H, Motoyama T, Hirai N, Kugiyama K, Ogawa H, Yasue H. Estradiol supplementation suppresses hyperventilation-induced attacks in postmenopausal women with variant angina. *J Am Coll Cardiol* 2001 Mar 1;37(3):735-740.
10. Tzivoni D, Keren A, Benhorin J, Gottlieb S, Atlas D, Stern S. Prazosin therapy for refractory variant angina. *Am Heart J* 1983 Feb;105(2):262-266.
11. Yoshida K, Inoue T, Hirakawa N, Node K. Endoscopic thoracic sympathectomy as a novel strategy for vasospastic angina refractory to medical treatments. *J Cardiol* 2008 Aug;52(1):49-52.

# Chapter 4

Journal of Nuclear Cardiology 2009 May-June;16(3):405-10

# Association between anxiety disorder and the extent of ischemia observed in cardiac syndrome X

I.A.C. Vermeltfoort[a], P.G.H.M. Raijmakers[a], D.A.M. Odekerken[b], A.F.M. Kuijper[b], A. Zwijnenburg[c], G.J.J. Teule[d]

a. Department of Nuclear Medicine & PET Research, VU University Medical Centre, Amsterdam, The Netherlands
b. Department of Cardiology, Spaarne Hospital, Hoofddorp, The Netherlands
c. Department of Nuclear Medicine, Spaarne Hospital, Hoofddorp, The Netherlands
d. Department of Nuclear Medicine & PET, University Hospital Maastricht, The Netherlands

# ABSTRACT

**Background:** A possible link between the heart and brain has been reported for cardiac syndrome X. Anxiety disorder could be a pathophysiological mechanism for this cardiac chest pain. To the authors' knowledge, a quantitative analysis correlating anxiety with the extent of ischemia has not been done.

**Methods and Results:** In this pilot study we evaluated 20 patients with typical chest pain and completely normal coronary angiograms. These patients were screened with the State Scale (SS) and Trait Scale (TS) of the State-Trait Anxiety Inventory (STAI). All patients underwent myocardial perfusion scintigraphic imaging. The scintigrams were scored by 3 experienced readers having no knowledge of the STAI screening results. Patients with a low trait anxiety had significantly less ischemic segments on the myocardial perfusion imaging than patients with a high trait anxiety ($1.8 \pm 1.9$ vs. $3.5 \pm 0.6$, $p<0.05$). For state anxiety no significant differences could be found.

**Conclusion:** Cardiac syndrome X patients with high trait anxiety are at risk of having more ischemia.

# INTRODUCTION

About 20 % of patients with anginal chest pain have normal coronary angiograms. (1, 2) The term "cardiac syndrome X " (CSX) was introduced to describe these patients. (3, 4) A subgroup of these patients has objective signs of ischemia, such as the classic downsloping ST-segment depression on exercise testing and/or a reversible defect detected by myocardial single-photon emission computed tomography (SPECT). (5-9)
The pathogenesis of cardiac syndrome X (CSX) remains uncertain. Two mechanisms have been proposed: ischemia caused by coronary microvascular dysfunction, and enhanced cardiac pain sensitivity ("sensitive heart" syndrome). (10)
Several studies found abnormalities consistent with ischemia in patients with syndrome X using scintigraphic myocardial perfusion imaging(5-9), thermodilution (11), nuclear magnetic resonance spectroscopy (12), intracoronary acetylcholine(13, 14), atrial pacing(15) and cardiac magnetic resonance (CMR) imaging. (16, 17) These CMR studies support the hypothesis of microvascular ischemia in CSX patients. There are also PET studies demonstrating a reduced coronary flow reserve in CSX patients. (18-20) On the other hand, a recent CMR study found no impairment of subendocardial blood flow response in CSX patients,(21) and a PET study by Rosen et al showed no differences in myocardial blood flow between CSX patients and healthy controls. (22)
In the last few years, attention has been paid to the effect of psychological factors on coronary artery disease (e.g. atherosclerosis) and cardiac neural mechanisms. (23) Previous work identified the importance of impaired myocardial blood flow, particularly in the microvascular bed, in relation to mental stress,(24, 25) and the phenomenon of endothelial dysfunction induced by mental stress has been described in CSX. (26) Furthermore, CSX patients have significantly higher levels of anxiety. (27)
Owing to the conflicting data regarding ischemia in CSX patients, and also the possible role of anxiety, we performed a pilot study to measure the extent of ischemia and anxiety levels in a group of CSX patients.

# METHODS

## Patients

The pilot study population consisted of 20 patients from the outpatient clinic of the cardiology department in a general hospital (February 2004-September 2004). All patients exhibited typical chest pain, positive exercise stress testing (0.1 mV horizontal or downsloping ST-segment depression of 80 msec after the J point) and/or a reversible perfusion defect on a myocardial single photon emission tomograph (SPECT). Furthermore, all patients had completely normal coronary angiograms (CAG's). This

was independently confirmed by two cardiologists in separate viewing sessions and without clinical information.

The patients' characteristics are given in table 1. None of the patients had a percutaneous transluminal coronary angioplasty (PTCA); coronary artery bypass grafting (CABG) or prior myocardial infarction; coronary spasm during the coronary angiography; absence of pain without medication; pregnancy; hypertension (defined as blood pressure over 140/90 mm Hg); diabetes (defined by a fasting glucose level above 7.8 mmol per litre or a random-sample glucose level above 11.1 mmol per litre); arrhythmias such as paroxysmal atrial fibrillation (PAF); left bundle branch block; valve dysfunction (other than mitral valve insufficiency grade 1); abnormal left ventricle ejection fraction ( LVEF<50 %) or other structural abnormalities of the heart. Also, none of the patients had electrographic signs of left ventricular hypertrophy (defined as a value above 35 mm for the sum of the height of the S wave in lead $V_1$ and the height of the R wave in lead $V_5$)(28), or any change in clinical condition between the investigations.

The study complied with the Declaration of Helsinki, the institutional ethics committee approved this study, and all patients gave written informed consent.

**TABLE 1**: patients' characteristics

| Patient's characteristics | Value |
|---|---|
| Age, mean ± SD (years) | 55 ± 11 |
| Women, n (%) | 14 (70%) |
| Smoker, n (%) | 3 (15%) |
| Hypertension | 0 (0%) |
| CAD in family | 13 (65%) |
| Hyperventilation | 1 (5%) |
| Time between onset angina and first visit cardiologist, mean ± SD (years) | 3.1 ± 8.1 |
| Number of coronary angiograms, mean ± SD | 1.2 ± 0.5 |
| Number of patients using cardiac drugs | 8 (40%) |
| Number of patients restricted in daily living due to angina pectoris | 6 (30%) |
| Number of patients restricted in sport due to chest pain | 5 (25%) |
| Number of patients experiencing chest pain during emotional stress | 7 (35%) |

## Screening for anxiety

Patients were recruited for a questionnaire study after their visit to the outpatient clinic of the cardiology department. State anxiety was measured by the State Scale (SS) and trait anxiety by the Trait Scale (TS) of the State-Trait Anxiety Inventory (STAI Dutch version revised by van der Ploeg, Defares and Spielberger). (29, 30) This self-report scale measures the current symptoms of anxiety (state scale) and the participants' predisposition to anxiety (trait scale). It consists of 2x20 self-report items, and earlier

use has shown good internal consistency (a = 0.87 – 0.92) and validity. For analysis, the subjects were categorized as having low (score<40) or high (score >40) state and trait anxiety. (31, 32)
For all the patients the questionnaires were supplemented by reviews of medical records and by a general questionnaire, including indices of socio-economic status (education, marital status, and current employment).

## Myocardial perfusion SPECT (stress-rest 2 days protocol)

The first day was allocated to the stress (exercise) study. Patients were instructed to stop all cardiac medication 24 hours before testing, and to have a light breakfast. They had not consumed caffeine-containing beverages for 24 hours before the test. An intravenous line of normal saline solution, with a 20-gauge cannula, was positioned in an antecubal vein. The exercise was performed on a calibrated ergometer using a symptom-limited test with stepwise increased work. A 12-lead electrocardiogram and blood pressure were monitored throughout the study. SPECT imaging was performed 45-60 minutes after peak exercise radiotracer injection.
On day two the patients underwent an at-rest study. Acquisition parameters were identical to those for the stress study.
SPECT imaging was performed on a double-headed gamma camera with a high-resolution collimator. A symmetric 20 % window was centred at 140 KeV, with a three-lead electric cardiographic monitoring. Imaging was acquired into a 64x64 computer matrix through a 180° rotation, with 32 positions; starting position is RAO 45°, with 8 frames per cycle. Bull's-eye generation, and visual analysis using a 19-segmental model were performed.
Three experienced observers interpreted the SPECT results. Perfusion was graded on a scale of 0 to 4, with 0 representing normal perfusion and 4 representing a very severe perfusion defect. Perfusion defects graded one or more points below the at-rest SPECT results were considered to be ischemic. Consensus was obtained in cases of disagreement. Also, the observers had not been informed of the STAI results.

## Statistical analysis

Variables like the STAI trait and state score, and the number of reversible segments in the SPECT study were expressed as mean ± standard deviation (SD). The numbers of patients (n) are expressed as absolute values and percentages of total (%). Variables were contrasted between 2 groups of low or high anxiety using an unpaired student test (two-sided), for both the state and the trait STAI groups. A p value less than 0.05 was considered to be significant.

# RESULTS

Table 2 lists the state anxiety and trait anxiety scores and the locations of ischemia on SPECT for all the patients.



## State STAI

Six (6) patients had high state anxiety levels. These patients had a mean of 3.0 ± 1.6 reversible perfusion defects on SPECT. This value was not significantly different from the mean of 2.0 ± 2.0 reversible perfusion defects for patients with low state anxiety levels.

**TABLE 2:** anxiety scores and location of ischaemia for individual patients

| patients | State anxiety | Trait anxiety | Number of ischaemic segments | Location of ischaemia |
|---|---|---|---|---|
| 1 | 53 | 52 | 3 | Anterior (m), apical |
| 2 | 34 | 36 | 1 | Anterior (b) |
| 3 | 20 | 20 | 4 | Posterolat(b), inferoseptal(b+m), inferior(m) |
| 4 | 27 | 24 | 0 | |
| 5 | 41 | 40 | 0 | |
| 6 | 51 | 56 | 4 | Anterior (d), posterolat (b+m+d) |
| 7 | 22 | 23 | 5 | Anterolat (b+m), anteroseptal (b+m+d) |
| 8 | 31 | 44 | 3 | Inferior (b), anterolat (b), apical |
| 9 | 52 | 58 | 3 | Inferior (b+m), posterolat (b+m) |
| 10 | 39 | 36 | 5 | Inferior (b+m), posterolat (b+m) |
| 11 | 24 | 26 | 0 | |
| 12 | 33 | 36 | 0 | |
| 13 | 39 | 34 | 2 | Inferior (b), posterolat (b) |
| 14 | 36 | 29 | 1 | Anteroseptal (b) |
| 15 | 41 | 44 | 4 | Anterior (b+m+d), anteroseptal (d) |
| 16 | 38 | 38 | 4 | Anterior (b+m), apical, anterolat (d) |
| 17 | 25 | 22 | 1 | Inferior (b) |
| 18 | 51 | 56 | 4 | Posterolat (b), inferior (b+m), apical |
| 19 | 24 | 24 | 0 | |
| 20 | 36 | 39 | 2 | Anteroseptal (m+d) |

State anxiety is considered increased with scores >40
Trait anxiety is considered increased with scores >40
B=basal, m=mid, d=distal segment

## Trait STAI

Six (6) patients had a high trait anxiety score, reflecting a high predisposition to anxiety. These patients had a mean of 3.5 ± 0.6 reversible perfusion defects on SPECT. This value was significantly different ($p < 0.05$) from the mean of 1.8 ± 1.9 reversible perfusion defects for patients with low trait anxiety scores**.** Figure 1 illustrates this difference.

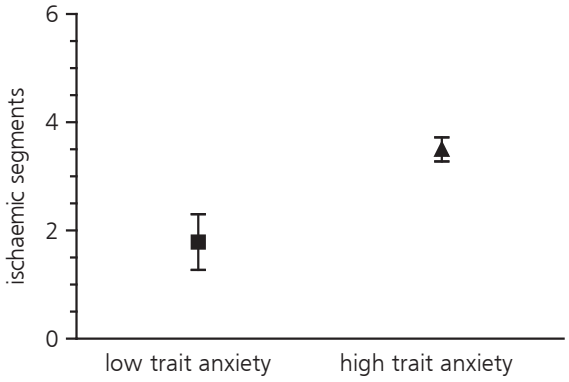



**FIGURE 1:** Patients with a high trait anxiety had significant more ischaemic segments on SPECT. Mean values ± SD

**TABLE 3:** characteristics of patients with high versus low trait anxiety

| Patient's characteristics | High Trait anxiety (n=6) | Low trait anxiety (n=14) | P value |
|---|---|---|---|
| Age, mean ± SD (years) | 55 ± 15 | 55 ± 9 | NS |
| Woman, % | 67 | 65 | NS |
| Smoker, % | 17 | 14 | NS |
| CAD in family, % | 33 | 78 | NS |
| Time between onset angina and first visit cardiologist, mean ±SD (years) | 2.2 ± 3.9 | 3.2 ± 9.1 | NS |
| Cardiac drugs, % | 33 | 43 | NS |
| Restricted in daily living due to angina pectoris, % | 50 | 21 | NS |
| Restricted in sport due to chest pain, % | 33 | 21 | NS |
| Chest pain during emotional stress, % | 67 | 21 | NS |

## Cross-sectional comparisons between those with high or low trait anxiety scores

Table 3 compares the patients with high and low scores for trait anxiety on the basis of demographic and medical variables. There is a trend for high trait anxiety patients to have more frequent chest pain during emotional stress, and they were also more frequently restricted in daily living as well as in practicing sports. However, none of the differences were statistically significant.

# DISCUSSION



This study demonstrates the association between high trait anxiety and the extent of ischemia in cardiac syndrome X patients. This suggests that trait anxiety is associated with an increased risk of exercise-induced ischemia and that high trait anxiety might be a predisposing risk factor for cardiovascular damage causing reversible perfusion defects on the SPECT imaging of CSX patients.

As mentioned in the introduction to this paper, attention has recently been paid to the effect of psychological factors on coronary artery disease and cardiac neural mechanisms. (23) Previous work identified the importance of impaired myocardial blood flow, particularly in the microvascular bed, in relation to ischemia induced by mental stress,(24, 25) and the phenomenon of endothelial dysfunction induced by mental stress has been described in CSX. (26)

Sudden emotional stress can lead to myocardial stunning in healthy subjects without CAD, probably owing to exaggerated sympathetic stimulation that causes vasoconstriction. (33) Similarly, increased sympathetic tone from mental stress can cause vasoconstriction in patients without coronary disease, such as in CSX. (33, 34)

The association between endothelial dysfunction and mental stress in CSX is reported in a SPECT study by Peix et al. (26) CSX patients were asked to focus on an incident in their lives that made them very angry, and SPECT imaging was done during this period of mental stress. A total of 6 out of 16 patients had SPECT-imaged reversible perfusion defects, and this correlated with more frequent endothelial dysfunction measured by brachial artery flow-mediated dilation.

A limitation of the study by Peix et al(26) is the non-standard mental stress test, since it cannot be assumed that the subjects were exposed to similar levels of mental stress. We have attempted in our pilot study to avoid this limitation by using validated standardized questionnaires for anxiety disorders to measure the anxiety predispositions and levels of each CSX patient. As mentioned earlier, state anxiety was measured by the State Scale (SS) and trait anxiety by the Trait Scale (TS) of the State-Trait Anxiety Inventory (STAI Dutch version revised by van der Ploeg, Defares and Spielberger). (29, 30)

Interestingly, a recent study of CAD patients showed that mental stress provokes a different myocardial ischemic response compared to exercise or adenosine. (35) However, there a little data available for patients groups with normal coronary arteries or syndrome X.

There are limited previous data on anxiety disorder and its relation to endothelial dysfunction. Narita et al. (36) used brachial artery flow measurements to investigate anxiety levels and endothelial dysfunction in elderly males. They found no link between high state anxiety levels and endothelial dysfunction, but there was a link for high trait anxiety. This result is broadly similar to that of our study, in which we showed that CSX

patients with high trait anxiety are at risk of having more extended ischemia compared to CSX patients with low trait anxiety.

### Reasons for differences in the state and trait anxiety results

(1) In our study, the lack of significance in the extent of ischemia between CSX patients with high and low state anxiety levels could have two reasons: firstly the small population of 20 patients, and secondly the time delay between state anxiety measurements and SPECT scanning. This latter possibility is because state anxiety levels may differ at different times. Obviously, a more definitive study involving a larger population is needed, whereby myocardial ischemia is investigated for state and trait anxiety levels at one time.

(2) A pathophysiological explanation for the different findings between the state and trait anxiety levels may be the different effects they have on the development of ischemia. State anxiety reflects a transitory emotional condition characterized by subjective feelings of tension, and is associated with heightened autonomic nervous system activity. Trait anxiety, on the other hand, reflects the existence of a certain predisposition to anxiety. A high predisposition to anxiety could reflect a chronic stress condition with long-term high anxiety levels. In turn, high anxiety levels are most probably a risk factor for cardiovascular damage only when they are sustained for long periods.

This hypothesis may also help to explain the results of Narita et al. (36), in particular their result that there was a significant association between trait anxiety and endothelial dysfunction for elderly males but not for young ones.

# CONCLUSIONS

This pilot study showed that CSX patients with high trait anxiety are at risk of having more extended ischemia compared to CSX patients with low trait anxiety. This suggests that anxiety-induced ischemia can occur in CSX patients, and that high trait anxiety might be a predisposing risk factor for cardiovascular damage causing reversible perfusion defects on the SPECT imaging of CSX patients

# ACKNOWLEDGEMENTS

We thank Dr R.J.H. Wanhill for his critical review and editing of the manuscript.

## Reference List




1. Bottcher M, Botker HE, Sonne H, Nielsen TT, Czernin J. Endothelium-dependent and -independent perfusion reserve and the effect of L-arginine on myocardial perfusion in patients with syndrome X. *Circulation* 1999 Apr 13;99(14):1795-1801.
2. Panza JA. Myocardial ischemia and the pains of the heart. *N Engl J Med* 2002 Jun 20;346(25):1934-1935.
3. Kemp HG, Jr., Vokonas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. *Am J Med* 1973 Jun;54(6):735-742.
4. Likoff W, Segal BL, Kasparian H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. *N Engl J Med* 1967 May 11;276(19):1063-1066.
5. Fragasso G, Rossetti E, Dosio F, Gianolli L, Pizzetti G, Cattaneo N, et al. High prevalence of the thallium-201 reverse redistribution phenomenon in patients with syndrome X. *Eur Heart J* 1996 Oct;17(10):1482-1487.
6. Hsu HB, Shiau YC, Kao A, Lin CC, Lee CC. Technetium-99m tetrofosmin myocardial perfusion single photon emission computed tomography in syndrome X: a preliminary report. *Jpn Heart J* 2003 Mar;44(2):153-162.
7. Kao CH, Wang SJ, Ting CT, Chen YT. Thallium-201 myocardial SPET in strictly defined syndrome X. *Nucl Med Commun* 1995 Aug;16(8):640-646.
8. Kao CH, Wang SJ, Ting CT, Chen YT. Tc-99m sestamibi myocardial SPECT in syndrome X. *Clin Nucl Med* 1996 Apr;21(4):280-283.
9. Tweddel AC, Martin W, Hutton I. Thallium scans in syndrome X. *Br Heart J* 1992 Jul;68(1):48-50.
10. Rosen SD, Camici PG. Syndrome X: Background, clinical aspects, pathophysiology and treatment. *G Ital Cardiol* 1994;24(6):779-790.
11. Cox ID, Botker HE, Bagger JP, Sonne HS, Kristensen BO, Kaski JC. Elevated endothelin concentrations are associated with reduced coronary vasomotor responses in patients with chest pain and normal coronary arteriograms 27. *J Am Coll Cardiol* 1999 Aug;34(2):455-460.
12. Buchthal SD, den Hollander JA, Merz CN, Rogers WJ, Pepine CJ, Reichek N, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med* 2000 Mar 23;342(12):829-835.
13. Motz W, Vogt M, Rabenau O, Scheler S, Luckhoff A, Strauer BE. Evidence of endothelial dysfunction in coronary resistance vessels in patients with angina pectoris and normal coronary angiograms 28. *Am J Cardiol* 1991 Oct 15;68(10):996-1003.
14. Egashira K, Inou T, Hirooka Y, Yamada A, Urabe Y, Takeshita A. Evidence of impaired endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary angiograms. *N Engl J Med* 1993 Jun 10;328(23):1659-1664.
15. Lanza GA, Luscher TF, Pasceri V, Shaw SG, Buffon A, Montenero AS, et al. Effects of atrial pacing on arterial and coronary sinus endothelin-1 levels in syndrome X 29. *Am J Cardiol* 1999 Nov 15;84(10):1187-1191.
16. Lanza GA, Buffon A, Sestito A, Natale L, Sgueglia GA, Galiuto L, et al. Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. *J Am Coll Cardiol* 2008 Jan 29;51(4):466-472.

17. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002 Jun 20;346(25):1948-1953.

18. de Vries J, DeJongste MJ, Jessurun GA, Jager PL, Staal MJ, Slart RH. Myocardial perfusion quantification in patients suspected of cardiac syndrome X with positive and negative exercise testing: a [13N]ammonia positron emission tomography study. *Nucl Med Commun* 2006 Oct;27(10):791-794.

19. Graf S, Khorsand A, Gwechenberger M, Schutz M, Kletter K, Sochor H, et al. Myocardial perfusion in patients with typical chest pain and normal angiogram. *Eur J Clin Invest* 2006 May;36(5):326-332.

20. Graf S, Khorsand A, Gwechenberger M, Novotny C, Kletter K, Sochor H, et al. Typical chest pain and normal coronary angiogram: cardiac risk factor analysis versus PET for detection of microvascular disease. *J Nucl Med* 2007 Feb;48(2):175-181.

21. Vermeltfoort IA, Bondarenko O, Raijmakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, et al. Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study. *Eur Heart J* 2007 Jul;28(13):1554-1558.

22. Rosen SD, Uren NG, Kaski JC, Tousoulis D, Davies GJ, Camici PG. Coronary vasodilator reserve, pain perception, and sex in patients with syndrome X. *Circulation* 1994 Jul;90(1):50-60.

23. Burg MM, Vashist A, Soufer R. Mental stress ischemia: present status and future goals. *J Nucl Cardiol* 2005 Sep;12(5):523-529.

24. Arrighi JA, Burg M, Cohen IS, Kao AH, Pfau S, Caulin-Glaser T, et al. Myocardial blood-flow response during mental stress in patients with coronary artery disease. *Lancet* 2000 Jul 22;356(9226):310-311.

25. Yeung AC, Vekshtein VI, Krantz DS, Vita JA, Ryan TJ, Jr., Ganz P, et al. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. *N Engl J Med* 1991 Nov 28;325(22):1551-1556.

26. Peix A, Trapaga A, Asen L, Ponce F, Infante O, Valiente J, et al. Mental stress-induced myocardial ischemia in women with angina and normal coronary angiograms. *J Nucl Cardiol* 2006 Jul;13(4):507-513.

27. Asbury EA, Creed F, Collins P. Distinct psychosocial differences between women with coronary heart disease and cardiac syndrome X. *Eur Heart J* 2004 Oct;25(19):1695-1701.

28. Zipes DP, Braunwald E. *Braunwald's heart disease a textbook of cardiovascular medicine*. 7th ed. ed. Philadelphia, PA: Elsevier Saunders; 2005.

29. van den Broek KC, Denollet J, Nyklicek I, van der Voort PH. Psychological reaction to potential malfunctioning of implantable defibrillators. *Pacing Clin Electrophysiol* 2006 Sep;29(9):953-956.

30. Verkuil B, Brosschot JF, Thayer JF. Capturing worry in daily life: are trait questionnaires sufficient? *Behav Res Ther* 2007 Aug;45(8):1835-1844.

31. Brans B, van den EF, Audenaert K, Vervaet M, van Daele K, van Heeringen C, et al. Depression and anxiety during isolation and radionuclide therapy. *Nucl Med Commun* 2003 Aug;24(8):881-886.

32. Britton JR. Maternal anxiety: course and antecedents during the early postpartum period. *Depress Anxiety* 2007 Mar 30.

33. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005 Feb 10;352(6):539-548.

34. Lacy CR, Contrada RJ, Robbins ML, Tannenbaum AK, Moreyra AE, Chelton S, et al. Coronary vasoconstriction induced by mental stress (simulated public speaking). *Am J Cardiol* 1995 Mar 1;75(7):503-505.

35. Hassan M, York KM, Li Q, Lucey DG, Fillingim RB, Sheps DS. Variability of myocardial ischemic responses to mental versus exercise or adenosine stress in patients with coronary artery disease. *J Nucl Cardiol* 2008 Jul;15(4):518-525.



36. Narita K, Murata T, Hamada T, Takahashi T, Kosaka H, Yoshida H, et al. Association between trait anxiety and endothelial function observed in elderly males but not in young males. *Int Psychogeriatr* 2007 Oct;19(5):947-954.

# Chapter 5

European Heart Journal 2007 Jul;28(13):1554-8

# Is subendocardial ischemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study

I.A.C. Vermeltfoort[1], O. Bondarenko[2], P.G.H.M. Raijmakers[1, 3], D.A.M. Odekerken[4], A.F.M. Kuijper[4], A. Zwijnenburg[5], M.J.E. van der Vis-Melsen[5], J.W.R. Twisk[3], A.M. Beek[2], G.J.J. Teule[1], A.C. van Rossum[2]

1. Department of Nuclear Medicine & PET Research, VU University Medical Centre, Amsterdam, The Netherlands
2. Department of Cardiology, VU University Medical Centre, Amsterdam, The Netherlands
3. Department of Clinical Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, The Netherlands
4. Department of Cardiology, Spaarne Hospital, Hoofddorp, The Netherlands
5. Department of Nuclear Medicine, Spaarne Hospital, Hoofddorp, The Netherlands

# ABSTRACT

**Aims:** Based upon a MRI study it has been suggested that subendocardial hypoperfusion is present in patients with cardiac syndrome X. However, further work is required to test whether these findings can be generalized.



**Methods and results:** MRI was used to visually and semi-quantitatively assess subendocardial and subepicardial perfusion, at rest and during an infusion of adenosine, in 20 patients with angina pectoris and normal coronary angiograms. A myocardial perfusion index (MPI) was calculated using the normalized upslope of myocardial signal enhancement. An index for myocardial perfusion reserve (MPRI) was calculated by dividing the MPI values at maximal vasodilatation by the values at rest.
The myocardial perfusion index (MPI) in our study population increased significantly during adenosine infusion in both the subendocardium (from 0.091 ± 0.020 to 0.143 ± 0.030: $p<0.001$) and the subepicardium (from 0.074 ± 0.017 to 0.135 ± 0.03: $p<0.001$). The overall MPRI was 1.83 ± 0.50.

**Conclusion:** The results show that patients with chest pain and normal coronary angiograms had significant perfusion responses to adenosine in both the subendocardium and subepicardium. In the present study we found no evidence for subendocardial hypoperfusion in these patients.

# INTRODUCTION

About 20 % of patients with anginal chest pain have normal coronary angiograms (1-5). The term "cardiac syndrome X" was introduced to describe these patients (6, 7). However, a subgroup of these patients has objective signs of ischaemia, such as the classic downsloping ST-segment depression on exercise testing and/or a reversible defect detected by myocardial single-photon emission computed tomography (SPECT)(8-13).
The pathogenesis of syndrome X is unclear. Physiological mechanisms have been proposed, such as the existence of myocardial ischemia that might be caused by coronary microvascular dysfunction or an abnormal pain perception (14). Several studies found abnormalities consistent with ischemia in patients with syndrome X using positron emission tomography (PET)(1), scintigraphic myocardial perfusion imaging (8, 11, 13), thermodilution (15), nuclear magnetic resonance spectroscopy (16), intracoronary acetylcholine (17, 18) and atrial pacing (19). However other investigators have questioned the proposed role of coronary microvascular dysfunction in syndrome X, Rosen et al found no differences in myocardial blood flow between syndrome X patients and healthy controls (20). Furthermore, in studies using stress echocardiography and myocardial metabolic measurements no evidence of ischemia was found in patients with syndrome X (4, 5, 20-24).
High resolution imaging with MRI offers the possibility to study subendocardial and subepicardial myocardial blood flow (25, 26). An interesting MRI study suggested the presence of subendocardial hypoperfusion in patients with syndrome X (27). The authors suggested that further work is required to test whether these findings can be generalized. To our knowledge the results of this study have not been confirmed. Therefore we employed MRI to visually and semi-quantitatively assess subendocardial and subepicardial perfusion, at rest and under stress during adenosine infusion in 20 patients with angina pectoris, objective signs of ischemia (ST segment depression during exercise test and/ or reversible defect on SPECT) and normal coronary angiograms.

# METHODS

## Patient characteristics and inclusion/exclusion criteria

We identified 34 patients with typical chest pain and normal coronary angiograms: 22 women and 12 men. All had established (1999 – 2004) exertional angina; an abnormal exercise electrocardiogram suggesting ischemia (0.1 mV horizontal or downsloping ST-segment depression of 80 msec after the J point) and/or a reversible perfusion defect on a myocardial SPECT; and completely normal results from coronary angiography, which was independently confirmed by two cardiologists in separate

viewing sessions and without clinical information. The mean time between coronary angiography and CMR was 11.6 months. Furthermore, the time between myocardial perfusion scintigraphy and coronary angiography was 2.5 months, the time between SPECT and CMR was 12.4 months.

The exclusion criteria were: a percutaneous transluminal coronary angioplasty (PTCA); coronary artery bypass grafting (CABG) or prior myocardial infarction; coronary spasm during the coronary angiography; absence of pain without medication; pregnancy; hypertension (defined as blood pressure over 140/90 mm Hg); diabetes (defined by a fasting glucose level above 7.8 mmol per litre or a random-sample glucose level above 11.1 mmol per litre); arrhythmias such as paroxysmal atrial fibrillation (PAF); left bundle branch block; valve dysfunction (other than mitral valve insufficiency grade 1); abnormal left ventricle ejection fraction ( LVEF<50 %) or other structural abnormalities of the heart. Furthermore, patients having general contra-indications for MRI according to the MR safe practice guidelines were also excluded (28). None of the patients had electrographic signs of left ventricular hypertrophy (defined as a value above 35 mm for the sum of the height of the S wave in lead $V_1$ and the height of the R wave in lead $V_5$) (29), or any change in clinical condition between the investigations.

Finally 20 of the 34 identified patients were selected for first pass contrast cardiovascular MR. These patients' characteristics are given in table 1. The reasons for excluding the other 14 patients from the MRI study were: absence of pain without medication (n=2); claustrophobia (n=8); 1 patient did not fit into the MRI scanner owing to obesity (height 167 cm, weight 120 kg); 1 patient cancelled due to negative advice from his physician; 1 patient had moved to an unknown address; and 1 patient's original coronary angiogram data were unavailable for the independent evaluation by two cardiologists. In addition to the characteristics in table 1, the selected patients were examined in more detail as follows, the SPECT results showed reversible perfusion defects in 16 patients, 1 patient had a reversed perfusion pattern, 1 patient showed normal perfusion, and a mild fixed defect was seen in 2 patients. An abnormal exercise electrocardiogram

**Table 1:** Patients' characteristics

| Characteristic | Value |
|---|---|
| Age, mean ± SD (years) | 55 ± 11 |
| Women, n (%) | 15 (75%) |
| Smoker, n (%) | 5 (28%) |
| Cholesterol, mean ± SD (mmol per litre) | 5.7 ± 1.7 |
| Glucose, mean ± SD (mmol/litre) | 5.1 ± 0.64 |
| Blood pressure systolic, mean (mm Hg) | 129 ± 15 |
| Blood pressure diastolic, mean (mm Hg) | 73 ± 8 |

suggesting ischaemia (0.1 mV horizontal or downsloping ST-segment depression of 80 msec after the J point) was present in 5 patients, 8 patients developed chest pain without significant ST-segment depression. The patients received hormonal replacement therapy (1 patient), calcium-channel blockers (7 patients), nitrates (4 patients), beta-blockers (6 patients), ACE inhibitors (1 patient), or no treatment (5 patients). These numbers reflect the fact that some patients received a combination of these drugs.
The study complies with the Declaration of Helsinki, institutional ethics committee approved this study, and all patients gave written informed consent.

## MRI scan protocol

The patients were instructed to stop all cardiac medication and refrain from caffeine-containing beverages 24 hours before cardiovascular MRI, and to eat light breakfast on the day of the test. Patients receiving beta-blocking drugs stopped their medication for at least three half life times. Before testing, an intravenous line of normal saline solution, with a 20-gauge canula was positioned in the antecubal veins in both arms. We used a single cannula for administration of contrast and a separate cannula for the administration of adenosine.
Imaging was performed with a 1.5T whole body MRI scanner (Magnetom Sonata, Siemens, Erlangen, Germany) using a four-element phased array cardiac receiver coil, and with the patient in a supine position. Scout images were acquired in the long axis and short axis orientations in order to specify the final short-axis views.
To obtain the first pass contrast enhanced images a saturation prepared single shot fast spoiled gradient echo pulse sequence was applied (repetition time 2.0 ms, echo time 1.0 ms, flip angle 12°, receiver band with 770 Hz/pixel, saturation delay 120 ms). The spatial resolution was 3-3.3 x 2.3 - 2.7 x 8 $mm^3$, with an image matrix of 128 x 73-93.
Perfusion scans were performed during the last minute of a 3-minute adenosine infusion (140 µg/kg/min) and 15 minutes later, at rest. Three short axis slices from apex to base at 25%, 50% and 75% of the end-systolic ventricular length were imaged. Both rest and stress perfusion images were acquired during breath-holding for 50 heartbeats and during the first pass of 0.05 mmol/kg gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany) flushed with 15 mL of 0.9% NaCL (flow rate 5 mL/s; Medrad, Spectris).
During the waiting period between the stress and rest perfusion scans, ECG-gated cine images were acquired using a breath-hold segmented steady-state free precession sequence. Cine bSSFP sequence parameters were a temporal resolution of 47 ms, excitation angle of 60°, receiver bandwidth 930 Hz/pixel, TR/TE of 3.1/1.6 ms, matrix 256 x 138-161 and voxel size of 1.3-1.4 x 1.8-2.0 x 5.0-6.0 $mm^3$ .
Per patient eight to ten short-axis views were obtained every 10 mm, starting from the mitral valve insertion and covering the entire left ventricle.

Late contrast-enhanced images, in order to definitely exclude myocardial scar tissue, were acquired 10 minutes after the last contrast injection in the same orientation as the first-pass contrast enhanced images, using a 2D segmented inversion recovery spoiled gradient-echo pulse sequence triggered to end-diastole (repetition time/echo time = 9.6/4.4 ms, flip angle 25°, number of excitations = 1, matrix 208 x 256, typical voxel size of 1.6 x 1.3 x 5.0 $mm^3$, receiver bandwidth 130 Hz/pixel). The inversion time was set to null the signal of normal myocardium, and was typically in the range of 220-290 ms.

## MRI Analysis

Analysis of the MR images was done both visually and semi-quantitatively. An 18-segment model was used, dividing the left ventricle into six basal, six midventricular, and six distal segments.

Qualitative assessment was by visual interpretation of the MR images by two observers. The SPECT and CMR analysis was performed separately. Observers of the SPECT and the observer of the CMR were blinded for the results of other diagnostic procedures.

First-pass perfusion contrast-enhanced MR images were assessed for the presence or absence of regions of reduced contrast uptake. Delayed contrast-enhanced images were assessed for the presence of any hyperenhancement. The degree of myocardial wall thickening was assessed from functional cine images.

Global function was assessed by calculating left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively) using planimetry of all short-axis images in each patient. Left ventricular ejection fraction (LVEF, in %) was calculated as (LVEDV – LVESV)/LVEDV.

Semi-quantitative analysis was performed using a dedicated software package (Mass 5.0, Medis, Leiden, The Netherlands). The endocardial and epicardial contours on perfusion images were traced**,** and corrected manually for cardiac motion. Each slice was divided into six equiangular segments, starting from the inferior septal insertion of the right ventricle. These segments were further subdivided into subendocardial and subepicardial regions, which were traced with their outer borders close to the endocardial and epicardial surfaces and inner borders adjacent to each other in the mid-wall. To obtain information about the input function, an additional region was drawn in the left ventricular cavity.

For each of the defined regions a curve was generated showing relative signal intensity plotted against time. The maximum upslopes of the myocardium and the left ventricular blood pool were determined using 5- and 3-point linear fits, respectively. The results for the myocardial regions were corrected for differences in the arterial input function of the contrast agent bolus by dividing the myocardial upslope by the left ventricular blood pool upslope (30). An index for myocardial perfusion reserve (MPRI) was calculated by dividing the values at maximal vasodilatation by the values at rest.

### Statistics

There was no sample size calculation. Due to the limited CMR capacity it was decided prior to the start of the study, to include 20 patients. For statistical analysis we used mean values of perfusion parameters of the subendocardial and subepicardial regions. In this section the summary values are presented as means ± SD. Differences between means in MPI and MPRI subendocardial and subepicardial of each patient were tested using paired student test (two-sided). A p value of less than 0.05 was considered to be significant.

## RESULTS

### Heart rates, blood pressure and chest pain

The baseline heart rate was 71 ± 11 BPM, increasing to 94 ± 14 BPM during adenosine infusion. The baseline blood pressure was systolic 139 ± 20 mm Hg and diastolic 80 ± 9 mm Hg. During maximum vasodilatation the blood pressure was systolic 140 ± 18 mm Hg and diastolic 73 ± 10 mm Hg. Furthermore 14 of the 20 patients experienced severe chest pain during adenosine infusion. The remaining 6 patients did not experience any chest pain.

### MRI visual analysis

All patients showed initial subendocardial signal reductions on the first pass cardiovascular MR images, which disappeared after approximately 5 heartbeats (see figure 1). This temporary signal loss is considered to be an artefact related to the first pass sequence and is not typical for an ischaemia related defect which shows a more sustained signal loss (31). These so-called dark rim artifacts were present in 93% of all the slice series, and in 44% of the slices series it was visible around the whole subendocardium.

In addition there were visual signs of ischaemia in 2 patients (in one patient a mid-anterior/mid-anteroseptal sustained transmural defect, and in the other a basal anterolateral and basal posterolateral sustained transmural defect). These signs were present in 4 segments out of a total of 360. In other words, only 1,1 % of the segments had visual signs of ischaemia. No hyperenhancement was seen on late contrast enhanced images.

### Global ventricular function

The mean LVEDV was159 ± 35 ml, mean LVESV was 70 ± 17 ml and the mean EF was 57 ± 3%.

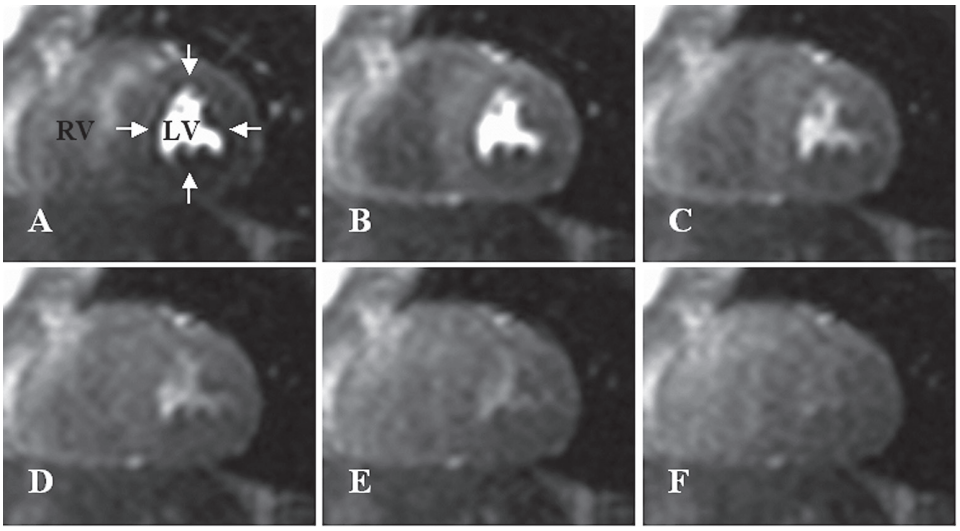



**FIGURE 1:** Midventricular short axis view during first pass of gadolinium during stress. Panel A and B show a subendocardial ring of low signal enhancement at the time of maximum signal enhancement in the left ventricular cavity. Serial images (C-F) show disappearance of this ring and subsequent homogeneous myocardial enhancement.

## MRI semi-quantitative analysis

The myocardial perfusion index (MPI) in our study population increased significantly during adenosine infusion in both the subendocardium and subepicardium: from 0.091 ± 0.020 to 0.143 ± 0.030 ($p<0.001$), and from 0.074 ± 0.017 to 0.135 ± 0.03 ($p<0.001$), respectively, (see figure 2). Note that in both the resting and stressed states the subendocardial MPI was higher than the subepicardial MPI: respectively 0.091 ± 0.020 versus 0.074 ± 0.017 ($p<0.001$), and 0.143 ± 0.030 versus 0.135 ± 0.03 ($p=0.021$).

An index for myocardial perfusion reserve (MPRI) was calculated as the ratio of the MPI during stress to the MPI at rest. The MPRI for the entire transmural extent of the myocardium was 1.83 ± 0.50. However, there was a significant difference between the MPRI in the subendocardium, 1.67 ± 0.38 and the subepicardium, 1.98 ± 0.64 ($p=0.001$).

The mean subendocardial**:** subepicardial MPRI ratio was 0.91 ± 0.11. None of the patients had a subendocardial**:** subepicardial MPRI ratio less than 0.72, which has been proposed as the optimal cut-off for distinguishing between normal controls and subendocardial hypoperfusion in patients with syndrome X (27).

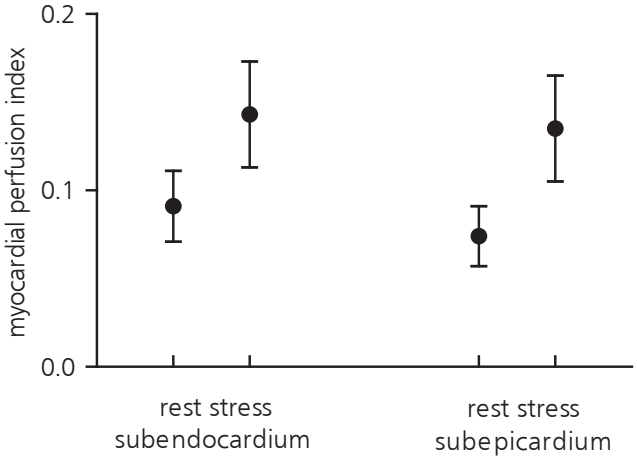



**FIGURE 2:** Myocardial perfusion index in patients with syndrome X in subendocardium and subepicardium.

# DISCUSSION

This study has shown that patients with chest pain and normal coronary angiograms had significant perfusion responses to adenosine in both the subendocardium and the subepicardium. Hence, we found no evidence for subendocardial ischaemia in our group of patients.

The adenosine-induced significant increases in subendocardium MPI, from 0.091 to 0.143, contrast with an earlier MRI study, where the MPI did not change significantly (27).

These MPI values found in our patient group at rest and under stress agree with the results from the control group in the study by Panting et al (27). Both studies found significant MPI increases in the subepicardium in response to adenosine. The selection of both patient populations is not exactly equal, this difference in selection may partially explain the different results we have found in patients with syndrome X (although the mean age and male/female distribution were similar). In our study more patients with syndrome X had an abnormal myocardial SPECT result, while in the study of Panting et al. more patients showed an abnormal ECG during exercise. However, the selection of syndrome X patients using both exercise- ECG and SPECT is an accepted method(12). As Lanza stated in an overview exercise-induced ST segment depression is not required. In patients with obstructive CAD, exercise electrocardiogram may be negative in patients with coronary microvascular disease, whereas findings compatible with myocardial ischemia could be detected by other diagnostic techniques (e.g. stress myocardial scintigraphy)(12).

In our study we found dark rim artefacts during the peak gadolinium concentration in the left ventricular blood-pool MRI images in all patients. This temporary signal loss is considered to be an artefact related to the first pass sequence and is not typical for an ischaemia related defect which shows a more sustained signal loss. These dark rims along parts of the subendocardial border of the left ventricle and the myocardium has been noticed in dynamic contrast-enhanced MR perfusion studies (31, 33). Several causes have been proposed for this so-called dark rim artefact, such as cardiac motion, Gibbs ringing due to limited spatial resolution and susceptibility. Considering the spatial resolution and the cardiac acquisition window applied in this study is not to be expected that we experienced more artifacts compared to the study of Panting et al (27).

We found no evidence for microvascular dysfunction in the subendocardium or subepicardium since both regions showed a clear increase in MPI during adenosine infusion.

This is in accordance with previous work with PET, which failed to show absolute myocardial perfusion abnormalities during pharmacological stress in syndrome X patients compared to normal controls (4, 20). Although absolute flow determination is difficult with MRI, we found small differences in the MPI between the subendocardial and subepicardial region of the left ventricle. In the resting state there was a 21 % higher MPI in the subendocardium compared to the subepicardium. This result might be explained by the higher workload of the subendocardial part of the left ventricle wall, which is in agreement with an experimental study of dogs by Hittinger et al., who observed a 31 % ± 7 % higher blood flow in the LV subendocardium compared to the subepicardial region for normal dogs in the resting state (34).

The pathogenesis of cardiac syndrome X is unclear. The main hypotheses for its occurrence are microvascular dysfunction or abnormal pain perception (2-4, 35). There have been conflicting data concerning the possible role of myocardial ischaemia in syndrome X. Several studies of patients with syndrome X demonstrated ischemia (1, 15-19), while other investigations found no confirmatory evidence of ischaemia during stress in these patients (5, 20-22). Alternative non-ischemic mechanisms of chest pain have been proposed in patients with cardiac syndrome X. In one study an abnormal pain perception has been reported, using pain provocation by catheter movement within the right atrium or ventricle (36). Another study showed specific cortical activation in the right anterior insula in patients with syndrome X and not in controls (37). The exact mechanism of chest pain in patients with syndrome X remains unclear since our data do not support the hypothesis of subendocardial ischemia in this patient group.

We consider the relative small number of patients and the frequent occurrence of subendocardial artifacts with CMR as the major study limitations.

Larger studies with newer CMR sequences and independent coronary flow measurements may increase the insight of subendocardial perfusion in syndrome X patients. Further studies are needed to reveal the cause of chest pain in this specific patient group.

## Concluding remarks

We conclude that our cardiovascular MRI study of patients with chest pain, positive exercise ECG stress testing and/or positive myocardial perfusion SPECT and normal coronary angiography, demonstrated significant adenosine-induced increases in both subendocardial and subepicardial myocardial perfusion indices (MPI). We found no evidence for specific subendocardial ischemia with MRI in this group of patients.

# ACKNOWLEDGEMENTS

O. Bondarenko is supported by the Netherlands Heart Foundation, grant number 2001B158.
Thanks to Dr R.J.H. Wanhill and M.B.M. Hofman Ph D, for their critical review of the manuscript.
**Conflict of Interest:** none declared.

## Reference List




1. Bottcher M, Botker HE, Sonne H, Nielsen TT, Czernin J. Endothelium-dependent and -independent perfusion reserve and the effect of L-arginine on myocardial perfusion in patients with syndrome X. *Circulation* 1999;99(14):1795-1801.
2. Panza JA. Myocardial ischemia and the pains of the heart. *N Engl J Med* 2002;346(25):1934-1935.
3. Crea F, Lanza GA. Angina pectoris and normal coronary arteries: cardiac syndrome X. *Heart* 2004;90(4):457-463.
4. Cannon RO, III, Camici PG, Epstein SE. Pathophysiological dilemma of syndrome X. *Circulation* 1992;85(3):883-892.
5. Camici PG, Marraccini P, Lorenzoni R, Buzzigoli G, Pecori N, Perissinotto A, Ferrannini E, L'Abbate A, Marzilli M. Coronary hemodynamics and myocardial metabolism in patients with syndrome X: response to pacing stress. *J Am Coll Cardiol* 1991;17(7):1461-1470.
6. Kemp HG, Jr., Vokonas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. *Am J Med* 1973;54(6):735-742.
7. Likoff W, Segal BL, Kasparian H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. *N Engl J Med* 1967;276(19):1063-1066.
8. Fragasso G, Rossetti E, Dosio F, Gianolli L, Pizzetti G, Cattaneo N, Fazio F, Chierchia SL. High prevalence of the thallium-201 reverse redistribution phenomenon in patients with syndrome X. *Eur Heart J* 1996;17(10):1482-1487.
9. Kao CH, Wang SJ, Ting CT, Chen YT. Thallium-201 myocardial SPET in strictly defined syndrome X. *Nucl Med Commun* 1995;16(8):640-646.
10. Hsu HB, Shiau YC, Kao A, Lin CC, Lee CC. Technetium-99m tetrofosmin myocardial perfusion single photon emission computed tomography in syndrome X: a preliminary report. *Jpn Heart J* 2003;44(2):153-162.
11. Kao CH, Wang SJ, Ting CT, Chen YT. Tc-99m sestamibi myocardial SPECT in syndrome X. *Clin Nucl Med* 1996;21(4):280-283.
12. Lanza GA. Cardiac syndrome X: a critical overview and future perspectives. *Heart* 2006.
13. Tweddel AC, Martin W, Hutton I. Thallium scans in syndrome X. *Br Heart J* 1992;68(1):48-50.
14. Rosen SD. Hearts and minds: psychological factors and the chest pain of cardiac syndrome X. *Eur Heart J* 2004;25(19):1672-1674.
15. Cox ID, Botker HE, Bagger JP, Sonne HS, Kristensen BO, Kaski JC. Elevated endothelin concentrations are associated with reduced coronary vasomotor responses in patients with chest pain and normal coronary arteriograms. *J Am Coll Cardiol* 1999;34(2):455-460.
16. Buchthal SD, den Hollander JA, Merz CN, Rogers WJ, Pepine CJ, Reichek N, Sharaf BL, Reis S, Kelsey SF, Pohost GM. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med* 2000;342(12):829-835.
17. Motz W, Vogt M, Rabenau O, Scheler S, Luckhoff A, Strauer BE. Evidence of endothelial dysfunction in coronary resistance vessels in patients with angina pectoris and normal coronary angiograms. *Am J Cardiol* 1991;68(10):996-1003.
18. Egashira K, Inou T, Hirooka Y, Yamada A, Urabe Y, Takeshita A. Evidence of impaired endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary angiograms. *N Engl J Med* 1993;328(23):1659-1664.

19. Lanza GA, Luscher TF, Pasceri V, Shaw SG, Buffon A, Montenero AS, Crea F, Maseri A. Effects of atrial pacing on arterial and coronary sinus endothelin-1 levels in syndrome X. *Am J Cardiol* 1999;84(10):1187-1191.

20. Rosen SD, Uren NG, Kaski JC, Tousoulis D, Davies GJ, Camici PG. Coronary vasodilator reserve, pain perception, and sex in patients with syndrome X. *Circulation* 1994;90(1):50-60.

21. Panza JA, Laurienzo JM, Curiel RV, Unger EF, Quyyumi AA, Dilsizian V, Cannon RO, III. Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. *J Am Coll Cardiol* 1997;29(2):293-301.

22. Nihoyannopoulos P, Kaski JC, Crake T, Maseri A. Absence of myocardial dysfunction during stress in patients with syndrome X. *J Am Coll Cardiol* 1991;18(6):1463-1470

23. Zouridakis EG, Cox ID, Garcia-Moll X, Brown S, Nihoyannopoulos P, Kaski JC. Negative stress echocardiographic responses in normotensive and hypertensive patients with angina pectoris, positive exercise stress testing, and normal coronary arteriograms. *Heart* 2000;83(2):141-146.

24. Cannon RO, III, Curiel RV, Prasad A, Quyyumi AA, Panza JA. Comparison of coronary endothelial dynamics with electrocardiographic and left ventricular contractile responses to stress in the absence of coronary artery disease. *Am J Cardiol* 1998;82(6):710-714.

25. Keijer JT, van Rossum AC, Wilke N, van Eenige MJ, Jerosch-Herold M, Bronzwaer JG, Visser CA. Magnetic resonance imaging of myocardial perfusion in single-vessel coronary artery disease: implications for transmural assessment of myocardial perfusion. *J Cardiovasc Magn Reson* 2000;2(3):189-200.

26. Wilke N, Simm C, Zhang J, Ellermann J, Ya X, Merkle H, Path G, Ludemann H, Bache RJ, Ugurbil K. Contrast-enhanced first pass myocardial perfusion imaging: correlation between myocardial blood flow in dogs at rest and during hyperemia. *Magn Reson Med* 1993;29(4):485-497.

27. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002;346(25):1948-1953.

28. Kanal E, Borgstede JP, Barkovich AJ, Bell C, Bradley WG, Felmlee JP, Froelich JW, Kaminski EM, Keeler EK, Lester JW, Scoumis EA, Zaremba LA, Zinninger MD. American College of Radiology White Paper on MR Safety. *AJR Am J Roentgenol* 2002;178(6):1335-1347.

29. Zipes DP, Braunwald E. *Braunwald's heart disease a textbook of cardiovascular medicine*. 7th ed. ed. Philadelphia, PA: Elsevier Saunders; 2005.

30. Nagel E, Klein C, Paetsch I, Hettwer S, Schnackenburg B, Wegscheider K, Fleck E. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. *Circulation* 2003;108(4):432-437.

31. Storey P, Chen Q, Li W, Edelman RR, Prasad PV. Band artifacts due to bulk motion. *Magn Reson Med* 2002;48(6):1028-1036.

32. Camici PG, Gistri R, Lorenzoni R, Sorace O, Michelassi C, Bongiorni MG, Salvadori PA, L'Abbate A. Coronary reserve and exercise ECG in patients with chest pain and normal coronary angiograms. *Circulation* 1992;86(1):179-186.

33. Di Bella EV, Parker DL, Sinusas AJ. On the dark rim artifact in dynamic contrast-enhanced MRI myocardial perfusion studies. *Magn Reson Med* 2005;54(5):1295-1299.

34. Hittinger L, Mirsky I, Shen YT, Patrick TA, Bishop SP, Vatner SF. Hemodynamic mechanisms responsible for reduced subendocardial coronary reserve in dogs with severe left ventricular hypertrophy. *Circulation* 1995;92(4):978-986.

35. Rosen SD. The pathophysiology of cardiac syndrome X–a tale of paradigm shifts. *Cardiovasc Res* 2001;52(2):174-177.

36. Cannon RO, III, Quyyumi AA, Schenke WH, Fananapazir L, Tucker EE, Gaughan AM, Gracely RH, Cattau EL, Jr., Epstein SE. Abnormal cardiac sensitivity in patients with chest pain and normal coronary arteries. *J Am Coll Cardiol* 1990;16(6):1359-1366.

37. Rosen SD, Paulesu E, Wise RJ, Camici PG. Central neural contribution to the perception of chest pain in cardiac syndrome X. *Heart* 2002;87(6):513-519.

# Chapter 6

The Open Nuclear Medicine Journal 2009 Jan (1):1-6

# Correlation of myocardial perfusion on cardiac magnetic resonance versus myocardial perfusion scintigraphy in cardiac syndrome X

Ilse A.C. Vermeltfoort[1] MD, Pieter G.H.M. Raijmakers[1] PhD, Olga Bondarenko[2] MD, Anton Zwijnenburg[3] PhD, Mark B.M Hofman[4] PhD, Gerrit J.J. Teule[5] PhD, Aernout M. Beek[2] MD, Albert C. van Rossum[2] PhD·

1. Department of Nuclear Medicine & PET Research, VU University Medical Center, Amsterdam, The Netherlands
2. Department of Cardiology, VU University Medical Center Amsterdam, The Netherlands
3. Department of Nuclear Medicine, Spaarne Hospital, Hoofddorp, The Netherlands
4. Department of Physics and Medical Technology, VU University Medical Centre Amsterdam, The Netherlands
5. Department of Nuclear Medicine, Maastricht University medical Centre, Maastricht, The Netherlands

# ABSTRACT



**Background** In cardiac syndrome X, which is a syndrome defined as chest pain, positive exercise stress testing and/or reversible myocardial perfusion defects during myocardial scintigraphy and normal coronary angiograms, the ischemic origin is still debated. No previous study compared the myocardial perfusion in stress first-pass cardiac magnetic resonance (CMR) versus stress single-photon emission computed tomography (SPECT) in cardiac syndrome X.

**Methods** We performed stress SPECT and CMR imaging for 20 syndrome X patients. Perfusion analysis of the CMR was done by using the normalized upslope of myocardial signal enhancement to derive the myocardial perfusion index (MPI) and the myocardial perfusion reserve index (MPRI). The SPECT images were visually scored by 3 observers using a segmental model.

**Results** An MPRI of ≤ 1.2 was found for 31 (9%) of the 335 segments, indicating local ischemia. SPECT indicated reversible perfusion defects for 39 (12%) of the 335 segments. However, the combination of both an MPRI of ≤ 1.2 and a reversible perfusion defect was detected in only 3 segments.

**Conclusions** Our data show about 10% stress-induced myocardial perfusion abnormalities on CMR and SPECT, suggesting local ischemia. However, only in 1% of the segments there was concordance for the presence of myocardial ischemia with both exams. This result may be evidence for the variability over time of the mechanisms responsible for coronary microvascular dysfunction.

# INTRODUCTION

About 20 % of patients with anginal chest pain have normal coronary angiograms (CAG). The term cardiac "syndrome X" was introduced to describe these patients. (1-3) A subgroup of these patients has objective signs of ischaemia, such as the classic downsloping ST-segment depression on exercise ECG testing and/or a reversible defect detected by myocardial Single Photon Emission Computed Tomography (SPECT). (4-9)
The pathogenesis of this syndrome is far from clear. Different diagnostic imaging modalities, myocardial perfusion SPECT, cardiac Positron Emission Tomography (PET) and Cardiovascular Magnetic Resonance (CMR) imaging, have been used to try and reveal the physiological mechanism. Important results include reversible defects with myocardial SPECT and CMR, indicating local ischaemia. (4-6, 8, 10) Another important CMR finding is subendocardial ischaemia in a group of syndrome X patients. The ischaemia was located in the whole subendocardial layer of the left ventricle. (11) Subendocardial ischaemia may explain the reversible defects seen in other studies. However the hypothesis of subendocardial ischemia in cardiac syndrome X patients was not supported by our earlier CMR study done with patients having chest pain and normal coronary angiograms. (12) On the other hand, in that study the myocardial perfusion indexes (MPI) were calculated for the whole subendocardial and the whole subepicardial layer. Hence, regional ischaemia could have been undiscovered owing to averaging segmental MPI calculations as one mean subendocardial MPI and one mean subepicardial MPI.
To our knowledge there has not been a study comparing SPECT results and stress CMR results in cardiac syndrome X patients. Therefore we studied a group of patients with angina pectoris and normal coronary arteries using both SPECT and CMR to determine whether local reversible SPECT defects correlated with locally decreased myocardial perfusion by CMR.

# MATERIALS AND METHODOLOGY

## Patient characteristics and inclusion/exclusion criteria

All 20 patients had an established (1999 – 2004) diagnosis of classic syndrome X, consisting of a typical history of exertional angina; an abnormal exercise electrocardiogram (0.1 mV horizontal or downsloping ST-segment depression of 80 msec after the J point) and/or a reversible perfusion defect on a myocardial SPECT; and completely normal findings from coronary angiography (CAG), which was independently evaluated by two cardiologists in separate viewing sessions and without knowledge of the clinical information.

The exclusion criteria were: percutaneous transluminal coronary angioplasty (PTCA); coronary artery bypass grafting (CABG) or prior myocardial infarction; spasm during the CAG reviewing; freedom from pain without medication; pregnancy; hypertension (defined as blood pressure over 140/90 mm Hg); diabetes (defined by a fasting glucose level above 7.8 mmol per litre or a random-sample glucose level above 11.1 mmol per litre); arrhythmias such as paroxysmal atrial fibrillation (PAF); left bundle branch block; valve dysfunction (other than mitral valve insufficiency grade 1); and abnormal left ventricular ejection fraction ( LVEF<50 %) or other structural abnormalities of the heart. Furthermore, patients having general contra-indications for CMR imaging according to the MR safe practice guidelines were also excluded. (13) Finally, none of the patients had electrocardiographic signs of left ventricular hypertrophy (defined as a value above 35 mm for the sum of the height of the S wave in lead $V_1$ and the height of the R wave in lead $V_5$), as later confirmed by CMR. None of the patients had any change in clinical condition or medication between the investigations.

Five patients had abnormal exercise electrocardiograms suggesting ischaemia. Eight patients showed an inconclusive exercise ECG test (chest pain without significant ST-segment depression).

The patients received calcium-channel blockers (7 patients), nitrates (4 patients), beta-blockers (6 patients), ACE inhibitors (1 patient), or no treatment (5 patients). These numbers reflect the fact that some patients received a combination of these drugs.

The study complied with the Declaration of Helsinki, was approved by the institutional ethics committee, and all patients gave written informed consent.

## Myocardial perfusion SPECT (stress-rest 2 days protocol)

Patients were instructed to stop all cardiac medication for 2 days. The exercise was performed on a calibrated ergometer using a symptom-limited test with stepwise increased work. A 12-lead electrocardiogram and blood pressure were monitored throughout the entire duration. SPECT imaging was performed 45-60 minutes after peak exercise radiotracer injection. Day two of this study was allocated to rest. The data acquisition parameters were identical for the rest and stress studies.

Bull's-eye generation with a visual analysis using a 19-segmental model was performed. Only 18 segments were used for comparison with the CMR. The apical segment was excluded because no myocardial perfusion was measured with CMR in the apical segment of the left ventricle.

All SPECT results were interpreted by three experienced observers, with any disagreements being resolved by consensus. This consensus method was used to avoid subjective individual SPECT results. These observers had no access to the results of the CMR study. Perfusion of both the stress and rest study was graded on a scale of 0 to 4, with 0 representing normal perfusion and 4 representing a very severe perfusion defect.

## CMR scan protocol (first pass stress-rest)

The patients were instructed to stop all cardiac medication and refrain from caffeine-containing beverages 24 hours before CMR imaging, and to eat a light breakfast on the day of the test. Patients receiving beta-blocking drugs stopped this medication for at least three drug half-lifetimes. Before testing, an intravenous line of normal saline solution, with a 20-gauge canula, was positioned in the antecubal veins in both arms. We used a single canula for administration of contrast and a separate canula for the administration of adenosine.

Imaging was performed with a 1.5T whole body MRI scanner (Magnetom Sonata, Siemens, Erlangen, Germany) using a four-element phased array cardiac receiver coil, and with the patient in a supine position. Scout images were acquired in the long axis and short axis orientations in order to specify the final short axis views.

To obtain the first pass contrast-enhanced images a saturation prepared single shot spoiled gradient-echo pulse sequence was applied (repetition time 2.0 ms, echo time 1.0 ms, flip angle 12°, receiver band with 770 Hz/pixel, saturation delay 120 ms). The spatial resolution was 3-3.3 x 2.3 - 2.7 x 8 $mm^3$, with an image matrix of 128 x 73-93. Perfusion scans were performed during the last minute of a 4-minute adenosine infusion (140 µg/kg/min), and at rest 15 minutes later. Three short axis slices from apex to base at 25%, 50% and 75% of the end-systolic ventricular length were imaged. Both stress- and rest-perfusion images were acquired during breath-holding for 50 heartbeats and during the first pass of 0.05 mmol/kg gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany) flushed with 15 ml of 0.9% NaCL (flow rate 5 ml/s; Medrad, Spectris).

During the waiting period between the stress- and rest-perfusion scans, ECG-gated cine images were acquired using a breath-hold segmented balanced steady-state free precession sequence (bSSFP). Eight to ten short-axis views were obtained every 10 mm, starting from the mitral valve insertion and covering the entire left ventricle. The cine bSSFP sequence parameters were a temporal resolution of 47 ms, excitation angle of 60°, receiver bandwidth 930 Hz/pixel, TR/TE of 3.1/1.6 ms, matrix 256 x 138-161 and voxel size of 1.3-1.4 x 1.8-2.0 x 5.0-6.0 $mm^3$.

To exclude myocardial scar tissue, late contrast-enhanced images were acquired 10 minutes after the last contrast injection and in the same orientation as the first pass contrast-enhanced images, using a 2D segmented inversion recovery spoiled gradient-echo pulse sequence triggered to end-diastole (repetition time/echo time = 9.6/4.4 ms, flip angle 25°, number of excitations = 1, matrix 208 x 256, typical voxel size of 1.6 x 1.3 x 5.0 $mm^3$, receiver bandwidth 130 Hz/pixel). The inversion time was set to null the signal of normal myocardium and was typically in the range of 220-290 ms.

### MRI Analysis

An 18-segment model was used, dividing the left ventricle into six basal, six midventricular, and six distal segments. The CMR analysis was performed separately from the SPECT analysis, and the CMR observer had no access to the results of the SPECT study and other diagnostic procedures. Delayed contrast-enhanced images were assessed for the presence of any hyper-enhancement.

Semi-quantitative analysis was done using a dedicated software package (Mass 5.0, Medis, Leiden, Netherlands). The endocardial and epicardial contours on perfusion images were traced and corrected manually for cardiac motion. Each slice was divided into six equiangular segments, starting from the inferior septal insertion of the right ventricle. These segments were further subdivided into subendocardial and subepicardial regions, which were traced with their outer borders close to the endocardial and epicardial surfaces, and inner borders adjacent to each other in the mid-wall. To obtain information about the input function, an additional region was drawn in the left ventricular cavity.

Curves showing relative signal intensity versus time were generated for each of the defined regions. The maximum upslopes of the myocardium and the left ventricular blood pool were determined using 5- and 3-point linear fits, respectively. The results for the myocardial regions were corrected for differences in the arterial input function of the contrast agent bolus by dividing the myocardial upslope by the left ventricular blood pool upslope (14). An index for myocardial perfusion reserve (MPRI) was calculated by dividing the MPI's at maximal vasodilatation by the values at rest. Segments with an MPRI $\leq$ 1.2 were considered to indicate ischaemia, as in the work of Ibrahim (15)

### Statistics

Following the SPECT segment scheme (but using only 18 instead of 19 segments, as mentioned earlier) we classified the CMR segments as non-ischaemic and ischaemic. Mean MPRI results were obtained for the transmural, subendocardial and subepicardial regions. The summary values are presented as means ± SD. Differences between the MPRI transmural, subendocardial and subepicardial non-ischaemic and ischaemic segments were tested using an unpaired student test whereby a p value of $< 0.05$ was considered significant.

## RESULTS

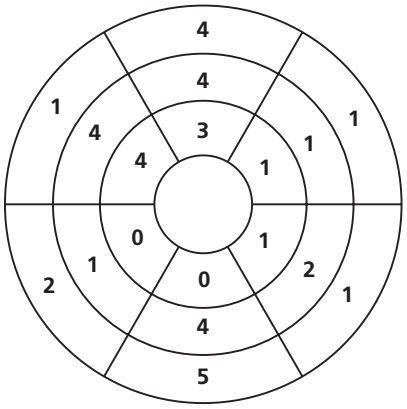
### Heart rates, blood pressure and chest pain

The baseline heart rate was 71 ± 11 BPM, increasing to 94 ± 14 BPM during adenosine infusion. The baseline blood pressure was systolic 139 ± 20 mm Hg and diastolic 80 ± 9

mm Hg. During maximum vasodilatation the blood pressure was systolic 140 ± 18 mm Hg and diastolic 73 ± 10 mm Hg. Furthermore, 14 of the 20 patients experienced severe chest pain during adenosine infusion. The remaining 6 patients did not experience any chest pain.

## SPECT visual analysis

The SPECT results showed reversible perfusion defects in 16 patients, a mild fixed defect in two patients, and one reversed perfusion pattern and one normal perfusion in the remaining two patients. The reversible perfusion defects were found in 47 (12%) of the 360 segments corresponding to all 20 syndrome X patients, see figure 1.




SPECT

**Figure 1:** Localisation and total number of reversible perfusion defect segments in 20 syndrome X patients

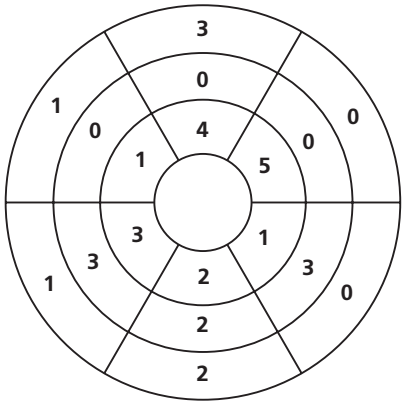
## CMR analysis

No hyper-enhancement was seen on the late contrast-enhanced images. A reliable myocardial perfusion index (MPI) during stress and rest could be measured for 335 (93%) of the 360 segments. MPI measurements for 25 (7%) of the segments were impossible owing to left ventricle outflow tract artefacts.

An index for myocardial perfusion reserve (MPRI) was calculated as the ratio of the MPI during stress to the MPI at rest. 31 (9.3%) of the 335 segments were assigned a transmural MPRI ≤ 1.2, indicating local ischaemia. see figure 2.

## Comparison of SPECT and CMR

Of a total of 4 reversible segments no reliable MPRI could be analysed, as it was planned to contain major parts of the left ventricular outflow tract (basal slice anterior and anterolateral). In 39 of the 335 segments also imaged by CMR (12%), a reversible perfusion defect was found with SPECT.




MPRI of ≤1.2

**FIGURE 2:** Localisation and total number of segments with a transmural Myocardial Perfusion Reserve Index (MPRI) ≤1.2 in 20 syndrome X patients.

Only 3 segments gave a matched result of a reversible perfusion defect and a transmural MPRI ≤1.2. 28 segments had a normal SPECT result combined with a low transmural MPRI (≤1.2) (mismatch); and 36 segments had an ischaemic SPECT result combined with a normal CMR (mismatch).

The summed bull's-eye of SPECT and CMR studies of these 20 patients show a similar distribution of ischaemic segments throughout the left ventricle, and there was no specific vascular territory with a high number of ischaemic segments. Analysis showed there was a lack of spatial correlation between the SPECT reversible perfusion defect segments and the MPRI ischaemic segments in each patient.

The mean transmural MPRI was the same in the normal and ischaemic SPECT segments 1.85 ± 0.65 versus 1.85 ± 0.58 (p = 1). Figure 3 shows that the mean subendocardial MPRI values were not different in the normal and ischaemic SPECT segments (1.68 ± 0.54 versus 1.70 ± 0.51, p = 0.860). Also, the mean subepicardial MPRI was similar in the normal SPECT segments versus ischaemic segments 2.01 ± 0.89 versus 2.00 ± 0.74 (p = 0.882).

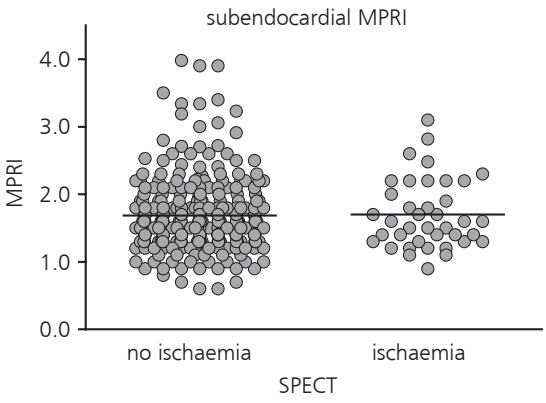



**FIGURE 3:** Mean subendocardial MPRI in the normal and ischaemic SPECT segments, SPECT= single-photon emission computed tomography

# DISCUSSION

We found evidence for local ischaemia in 10% of the left ventricle area with both the CMR study and the SPECT study. However, there was no spatial match for ischaemia detected by SPECT and CMR for these CSX patients. Only 3 segments out of 335 (1%) were concordant in both exams. Mismatches were present in 64 segments, mutually revealing ischaemia by one technique and a normal result by the other technique. Furthermore, SPECT-derived normal and ischaemic segments had similar mean myocardial perfusion reserve indexes (MPRI). In the light of these results, we conclude that for this group of patients local ischaemia was unlikely to be present in a fixed area of the left ventricle, Furthermore, it is unlikely that in this group of patients ischaemia was caused by a fixed anatomically or functionally abnormal vessel. On the other hand, the local ischaemia found with two independent techniques at different times could be explained by transient ischaemia. Local ischaemia might be present in a patient at different locations over time, a phenomenon that we speculatively describe as migrating ischaemia.

These results do not necessarily conflict with our earlier analysis, in which CMR detected significant increases of the myocardial perfusion both in the subendocardial and subepicardial layer. (16) Calculation of an average MPI for the whole subendocardial layer may mask local ischaemia in smaller segmental area's. Segmental analysis of the MPI may be more accurate than calculations of whole subendo- or subepicardial layers, especially since these layers will receive blood supply from different coronary vessels.

To our knowledge this is the first study directly comparing myocardial perfusion by stress SPECT and CMR imaging on a segmental basis for the same cardiac syndrome X patients in the same territories. Our transient ischaemic findings may be consistent with the arguments of Maseri et al. (16) These investigators speculated that distal to the most constricted microvessels there could be a patchy distribution of small foci of ischaemia which, when confluent, might be sufficient to cause transient ST-segment depression and also myocardial perfusion abnormalities. (16) Some support for this view is provided by a study by Osamichi et al. using PET and histopathology. They showed extensive myocardial $^{18}$F-fluorodeoxyglucose (FDG) uptake in combination with irregular narrowing of the coronary microvessels at the level of capillaries as well as meta-arterioles in syndrome X patients. (17) Such a patchy distribution of microvascular dysfunction might be responsible for the segmental SPECT and CMR abnormalities in the present study, hence suggesting microvascular migrating or transient ischaemia in cardiac syndrome X patients.

Our study is apparently partly at variance with the recent study by Lanza et al in which they found a relation between subendocardial perfusion defects with CMR and a reduced coronary flow reserve by coronary doppler in the same (anterior) region. (10)

However, no quantitative CMR analysis was performed. On the other hand, the Lanza study found reduced coronary flow reserve in the LAD coronary artery in 2 patients (11%) who displayed reversible perfusion defects with CMR only in the right coronary artery territory. This suggests a variability over time of the mechanisms responsible for the coronary microvascular dysfuntion (10), which is in line with our study, although in our population it is more frequently occurring.

Variations in the SPECT and CMR measurements in the present study may have contributed to the differences we found between the results of the two measurement techniques. This is despite our efforts to reduce the likelihood of variations and false positive results by using a consensus reading for the SPECT studies and a strict cut-off level for the MPRI calculations. For example, an MPRI of less than 1.2 indicates a clearly limited increase of myocardial perfusion, which is compatible with a more than 75% obstruction of coronary flow (15).Another potential limitation of the present study is the use of two different forms of stress testing for CMR and SPECT. However, for detection of ischaemia both types of stress testing give good results. An additional explanation for mismatched non-ischaemic and ischaemic segments comes from necessarily using the two techniques at different times. There were, however, no changes in cardiac medication, complaints, or changes in possible confounding factors like smoking. Furthermore, reversibility of anatomical changes of epicardial vessels is rather unlikely in patients with angina pectoris.

With regard to the techniques themselves, we assumed that CMR would be able to detect more ischaemia missed by SPECT owing to the higher spatial resolution of CMR (18). ur results do not support this assumption, since we found a comparable percentage of ischaemic segments with both techniques. The accuracy of quantitative first-pass perfusion CMR imaging using adenosine-induced hyperaemia has been demonstrated in several recent studies (14, 19), and nuclear myocardial perfusion imaging with SPECT is widely accepted as a standard evaluation of myocardial perfusion. However, our comparison of CMR with SPECT may not have been optimal. For example, the apical segment was not assessed by CMR and was excluded from this comparison. Thus our study lacks a direct comparison of CMR and SPECT in the apex. Also, the segments used by the segmental SPECT model were somewhat larger than the segments used in the CMR analysis. Nevertheless, it is unlikely that the above-mentioned differences explain the 95% mismatch of ischaemic segments. Furthermore, studies state that first pass CMR and myocardial perfusion SPECT correlate well and demonstrate fair-to-good agreement (70–90%) in the assessment of perfusion defects. (20-23)

# CONCLUSIONS

In conclusion, our data show about 10% stress-induced myocardial perfusion abnormalities on CMR and SPECT, suggesting local ischaemia in cardiac syndrome X patients. We found no evidence for ischaemia in fixed areas of the left ventricle in syndrome X. We speculate that our results may be compatible and explicable with a coronary microvascular dysfunction that is variable over time, as recently stated by Lanza (10). Further studies are necessary to confirm this hypothesis.

**Conflict of Interest:** None declared

# ACKNOWLEDGEMENTS

O. Bondarenko is supported by the Netherlands Heart Foundation, grant number 2001B158.

Thanks to Dr R.J.H. Wanhill for his critical review of the manuscript. Thanks to D.A.M Odekerken and A.F.M. Kuijper PhD for collecting the patients.

## Reference List




1. Kemp HG, Jr. Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. *Am J Cardiol* 1973 Sep 7;32(3):375-376.
2. Kemp HG, Jr., Vokonas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. *Am J Med* 1973 Jun;54(6):735-742.
3. Likoff W, Segal BL, Kasparian H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. *N Engl J Med* 1967 May 11;276(19):1063-1066.
4. Fragasso G, Rossetti E, Dosio F, Gianolli L, Pizzetti G, Cattaneo N, et al. High prevalence of the thallium-201 reverse redistribution phenomenon in patients with syndrome X. *Eur Heart J* 1996 Oct;17(10):1482-1487.
5. Kao CH, Wang SJ, Ting CT, Chen YT. Thallium-201 myocardial SPET in strictly defined syndrome X. *Nucl Med Commun* 1995 Aug;16(8):640-646.
6. Kao CH, Wang SJ, Ting CT, Chen YT. Tc-99m sestamibi myocardial SPECT in syndrome X. *Clin Nucl Med* 1996 Apr;21(4):280-283.
7. Kaul S, Newell JB, Chesler DA, Pohost GM, Okada RD, Boucher CA. Quantitative thallium imaging findings in patients with normal coronary angiographic findings and in clinically normal subjects. *Am J Cardiol* 1986 Mar 1;57(8):509-512.
8. Tweddel AC, Martin W, Hutton I. Thallium scans in syndrome X. *Br Heart J* 1992 Jul;68(1):48-50.
9. Lanza GA. Cardiac syndrome X: a critical overview and future perspectives. *Heart* 2007 Feb;93(2):159-166.
10. Lanza GA, Buffon A, Sestito A, Natale L, Sgueglia GA, Galiuto L, et al. Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. *J Am Coll Cardiol* 2008 Jan 29;51(4):466-472.
11. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002 Jun 20;346(25):1948-1953.
12. Vermeltfoort IA, Bondarenko O, Raijmakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, et al. Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study. *Eur Heart J* 2007 Jul;28(13):1554-1558.
13. Kanal E, Borgstede JP, Barkovich AJ, Bell C, Bradley WG, Felmlee JP, et al. American College of Radiology White Paper on MR Safety. *AJR Am J Roentgenol* 2002 Jun;178(6):1335-1347.
14. Nagel E, Klein C, Paetsch I, Hettwer S, Schnackenburg B, Wegscheider K, et al. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. *Circulation* 2003 Jul 29;108(4):432-437.
15. Ibrahim T, Nekolla SG, Schreiber K, Odaka K, Volz S, Mehilli J, et al. Assessment of coronary flow reserve: comparison between contrast-enhanced magnetic resonance imaging and positron emission tomography. *J Am Coll Cardiol* 2002 Mar 6;39(5):864-870.
16. Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. *J Am Coll Cardiol* 1991 Feb;17(2):499-506.
17. Osamichi S, Kouji K, Yoshimaro I, Tadashi U, Hiroichi T, Seiyu K, et al. Myocardial glucose metabolism assessed by positron emission tomography and the histopathologic findings of microvessels in syndrome X. *Circ J* 2004 Mar;68(3):220-226.

18. Wagner A, Mahrholdt H, Sechtem U, Kim RJ, Judd RM. MR imaging of myocardial perfusion and viability. *Magn Reson Imaging Clin N Am* 2003 Feb;11(1):49-66.

19. Al Saadi N, Nagel E, Gross M, Bornstedt A, Schnackenburg B, Klein C, et al. Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. *Circulation* 2000 Mar 28;101(12):1379-1383.

20. Keijer JT, van Rossum AC, van Eenige MJ, Bax JJ, Visser FC, Teule JJ, et al. Magnetic resonance imaging of regional myocardial perfusion in patients with single-vessel coronary artery disease: quantitative comparison with (201)Thallium-SPECT and coronary angiography. *J Magn Reson Imaging* 2000 Jun;11(6):607-615.

21. Matheijssen NA, Louwerenburg HW, van Rugge FP, Arens RP, Kauer B, de Roos A, et al. Comparison of ultrafast dipyridamole magnetic resonance imaging with dipyridamole SestaMIBI SPECT for detection of perfusion abnormalities in patients with one-vessel coronary artery disease: assessment by quantitative model fitting. *Magn Reson Med* 1996 Feb;35(2):221-228.

22. Fenchel M, Helber U, Simonetti OP, Stauder NI, Kramer U, Nguyen CN, et al. Multislice first-pass myocardial perfusion imaging: Comparison of saturation recovery (SR)-TrueFISP-two-dimensional (2D) and SR-TurboFLASH-2D pulse sequences. *J Magn Reson Imaging* 2004 May;19(5):555-563.

23. Thiele H, Plein S, Breeuwer M, Ridgway JP, Higgins D, Thorley PJ, et al. Color-encoded semiautomatic analysis of multi-slice first-pass magnetic resonance perfusion: comparison to tetrofosmin single photon emission computed tomography perfusion and X-ray angiography. *Int J Cardiovasc Imaging* 2004 Oct;20(5):371-384.

# Chapter 7

accepted Journal of Nuclear Cardiology

# Feasibility of subendocardial and subepicardial myocardial perfusion measurements in healthy normals with $^{15}O$-labeled water and positron emission tomography

Ilse A. Vermeltfoort[1], Pieter G. Raijmakers[1], Mark Lubberink[1], Tjeerd Germans[2], Albert C. van Rossum[2], Adriaan A. Lammertsma[1], Paul Knaapen[2]

1. Department of Nuclear Medicine & PET Research, VU University Medical Centre, Amsterdam, the Netherlands
2. Department of Cardiology, VU University Medical Centre, Amsterdam, the Netherlands

# ABSTRACT



**Background:** Positron emission tomography (PET) enables robust and reproducible measurements of myocardial blood flow (MBF). However, the relatively limited resolution of PET till recently prohibited distinction between the subendocardial and subepicardial layers in non-hypertrophied myocardium. Recent developments in hard- and software, however, have enabled to identify a transmural gradient difference in animal experiments. The aim of the present study was to determine the feasibility of subendocardial and subepicardial MBF in normal human hearts assessed with $^{15}$O-labeled water PET.

**Methods:** Twenty-seven healthy subjects (mean age 41 ± 13 years; 11 men) were studied with $^{15}$O-labeled water PET to quantify resting and hyperaemic (adenosine) MBF at a subendocardial and subepicardial level. In addition cardiac magnetic resonance imaging was performed to determine left ventricular (LV) volumes and function.

**Results:** Mean rest MBF was 1.46 ± 0.49 in the subendocardium, and 1.14 ± 0.342 $ml \cdot min^{-1} \cdot g^{-1}$ in the subepicardium ($p<0.001$). MBF during vasodilation was augmented to a greater extent at the subepicardial level (subendocardium vs. subepicardium: 3.88 ± 0.86 vs. 4.14 ± 0.88 $ml \cdot min^{-1} \cdot g^{-1}$, $p=0.013$). The endocardial-to-epicardial MBF ratio decreased significantly during hyperaemia (1.35 ± 0.23 to 1.12 ± 0.20, $p<0.001$). Hyperaemic transmural MBF was inversely correlated with left ventricular end-diastolic volume index (LVEDVI) ( $r^2=0.41$, $p=0.0003$), with greater impact however at the subendocardial level.

**Conclusions**: $^{15}$O-labeled water PET enables MBF measurements with distinction of the subendocardial and subepicardial layers in the normal human heart and correlates with LVEDVI. This PET technique may prove useful in evaluating patients with signs of ischaemia due to coronary artery disease or microvascular dysfunction.

# INTRODUCTION

The subendocardium is most susceptible to perfusion impairment and ischaemia principally occurs in the subendocardium before advancing to the subepicardial layer. (1) Subendocardial perfusion imaging may therefore be an important technique to enhance the sensitivity for detection of myocardial ischaemia. Presently, quantification of regional myocardial blood flow (MBF) is available with tracers such as $^{15}$O-labeled water ($H_2{}^{15}O$) and positron emission tomography (PET). $H_2{}^{15}O$ PET may therefore serve as a tool for quantifying impairments in microcirculatory vasodilator reactivity.(2, 3) Recent advances in cardiac PET hard- and software enable to distinguish between perfusion of the subendocardial and subepicardial layers in animal experiments and patients with left ventricular hypertrophy. (4, 5) However, data in normal human hearts are scarce. We studied the feasibility of subendocardial and subepicardial MBF measurements in a group of healthy volunteers using $H_2{}^{15}O$ PET during both rest and vasodilator stress.

# METHODS

## Patient population

Twenty-seven healthy subjects were studied. None of the patients had a history of cardiovascular disease, all were non-smokers, and none had any other cardiovascular risk factor. Accordingly, none of the volunteers was receiving any form of treatment. All underwent a physical examination, electrocardiography, laboratory analysis, and echocardiography revealing no abnormalities. The characteristics of the study group

**TABLE 1** Characteristics of normal subjects (n=27)

| Characteristics | Mean ± SD |
|---|---|
| Age (y) | 41 ± 13 |
| Sex (M/F) | 11/16 |
| LVEF (%) | 61 ± 5 |
| LVESV (ml) | 71 ± 17 |
| LVEDV (ml) | 180 ± 34 |
| Mean LV mass (g) | 96 ± 24 |
| Length (cm) | 177 ± 9 |
| Weight (kg) | 74 ± 13 |
| BSA ($m^2$) | 1.9 ± 0.2 |

LVEDV= left ventricular end-diastolic volume, LVEF= left ventricular ejection fraction, LVESV= left ventricular end-systolic volume, BSA= body surface area

are given in Table 1. All subjects gave written informed consent, and the protocol was approved by the Medical Ethics Committee of the VU University Medical Centre.

## Imaging protocol



***PET***. All scans were performed in 2D mode using an ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN, USA). The subjects were monitored constantly with single-lead electrocardiography, and blood pressure was measured every minute. After a transmission scan, 1100 MBq of $H_2{}^{15}O$ was injected intravenously under resting conditions and subsequently during pharmacologically induced hyperaemia (adenosine, 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$), as described previously in detail.(4, 6) Emission data were corrected for physical decay of $^{15}O$ and for dead time, scatter, randoms, and photon attenuation. The $H_2{}^{15}O$ emission sinograms were reconstructed using filtered back-projection with a Hanning filter at 0.5 of the Nyquist frequency, resulting in a transaxial spatial resolution of ~6.5 mm full-width at half-maximum.

***Cardiac magnetic resonance (CMR) imaging.*** Scans were performed on a 1.5-T whole body scanner (Magnetom Sonata, Siemens, Erlangen, Germany) using a six-element phased-array radio-frequency receiver body coil. All images were electrocardiographically gated and acquired during repeated breath holds in mild expiration of 10–15s, depending on heart rate. After localization of scout scans, cine images were acquired with a segmented balanced steady-state free-precession sequence. The image parameters were as follows: 5 mm slice thickness, 5 mm slice gap, <50 ms temporal resolution, 3.2 ms repetition time, 1.54 ms echo time, 60° flip angle, and 1.3 x 1.6 mm typical image resolution. After three long-axis view cines (2-, 3-, and 4-chamber views), a stack of 10–12 LV short-axis cines were acquired for full coverage of the LV).(7)

## Data analysis

***PET.*** Transaxial parametric MBF images were generated as described previously.(8) These images were reoriented according to the anatomic axis of the heart, and displayed as short-axis slices. The same reslicing parameters were applied to the dynamic $H_2{}^{15}O$ images. Regions of interest (ROIs) on these images were defined as septal, anterior, lateral, and inferior walls of the LV in the basal, mid, and apical planes, based on the 16-segment model of the AHA/ACC.(9) Additional ROIs were defined for the LA and right ventricular chamber. This latter set of ROIs was projected onto the dynamic $H_2{}^{15}O$ images to generate image-derived input functions. The standard single-tissue compartment model, together with these input functions, was used to determine MBF ($ml \cdot min^{-1} \cdot g^{-1}$ of perfusable tissue) for all myocardial tissue time-activity curves. The subendocardial and subepicardial layers were identified by dividing the myocardial

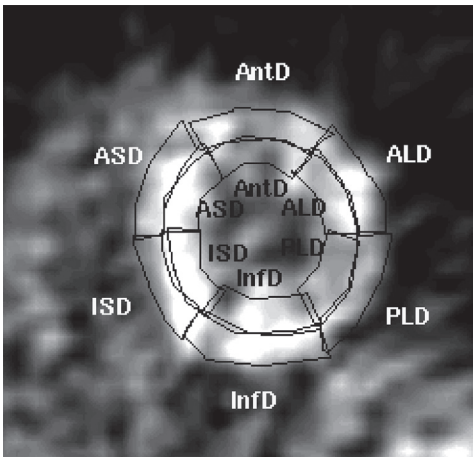



**FIGURE 1:** Example of delineation of subendocardial and subepicardial border on a parametric MBF image in short axis view at the midventricular level.

ROIs by a central line (Figure 1). Coronary flow reserve (CFR) was calculated as the ratio of hyperaemic to resting MBF. A subendocardial to subepicardial MBF ratio was additionally calculated. Because resting MBF is determined by cardiac workload, global baseline MBF corrected for the rate pressure product (RPP) was also calculated (MBF/RPP) x $10^4$.(10) Coronary vascular resistance (CVR) was calculated as the ratio of mean arterial pressure to MBF for both the subendocardial and subepicardial layers of the myocardium.(3)

***CMR imaging.*** Epicardial and endocardial contours were manually drawn on all end-diastolic (ED) and end-systolic (ES) LV short-axis images for LV volume analysis. Global LV function parameters, including ED Volume (LVEDV), ED volume adjusted for bsa (LVEDVI), ES volume (LVESV), ejection fraction (LVEF), and myocardial mass, were derived from epicardial and endocardial contours on the cine images by using of the MASS software package (Mass 5.0, Medis, Leiden, The Netherlands).

## Statistics

Values are expressed as means ± SD. For comparison of two data sets, a paired or unpaired Student's *t*-test was performed where appropriate. Multiple data sets were compared using multivariate ANOVA, and specific differences were identified by a Student's *t*-test corrected for multiple comparisons with the Bonferroni inequality adjustment. Linear regression was used to analyze the relationships between variables. All analyses were performed using SPSS 14 (SPSS, Chicago, IL, USA). Significant differences were defined as $p < 0.05$.

# RESULTS

## Haemodynamic parameters



Baseline heart rate was 65 ± 11, increasing to 98 ± 14 BPM during adenosine infusion ($p<0.001$). Baseline systolic blood pressure was 122 ± 15, and diastolic blood pressure 71 ± 10 mm Hg. During maximum vasodilatation, systolic blood pressure decreased to 117 ± 15 and diastolic blood pressure to 64 ± 7 mm Hg (both $p<0.05$ vs. baseline).

## Transmural MBF

Global resting transmural myocardial blood flow was 1.20 ± 0.31 and increased during hyperaemia to 3.94 ± 0.78 $ml \cdot min^{-1} \cdot g^{-1}$ ($p=0.001$), yielding a CFR of 3.28 ± 0.83. Global baseline MBF corrected for rate pressure product was 1.53 ± 0.34 $ml \cdot min^{-1} \cdot g^{-1}$.

## Regional transmural heterogeneity

Baseline transmural MBF for anterior, lateral, inferior, septum, and segments was 1.30 ± 0.39, 1.29 ± 0.37, 1.08 ± 0.32, and 1.11 ± 0.33 $ml \cdot min^{-1} \cdot g^{-1}$, respectively ($p=0.042$ by ANOVA). Hyperaemic MBF increased to 3.54 ± 0.93, 4.18 ± 0.90, 3.66 ± 1.04, and 4.10 ± 0.96 $ml \cdot min^{-1} \cdot g^{-1}$ for the different regions, respectively ($p=0.035$ by ANOVA). Transmural CFR for anterior, lateral, inferior and septum segments was 2.91 ± 0.91, 3.85 ± 1.15, 3.39 ± 0.74, and 3.67 ± 1.39 ($p=0.011$ by ANOVA, using post hoc bonferroni significant difference between septum vs. anterior $p=0.010$).

## Subendocardial vs. Subepicardial MBF

As shown in Figure 2 and listed in Table 2, the subendocardium displayed a significantly higher mean resting flow level of 1.46 ± 0.49 compared to the mean subepicardium level of 1.14 ± 0.42 $ml \cdot min^{-1} \cdot g^{-1}$ ($p<0.001$), with an endocardial-to-epicardial ratio of

**TABLE 2.** Subendocardial (Endo) en subepicardial (Epi) myocardial blood flow (ml • min-1 • g-1) and coronary flow reserve (CFR)

| | Rest | | | |
|---|---|---|---|---|
| | **Endo** | **Epi** | **p** | **Endo / Epi** |
| **Average** | 1.46±0.49 | 1.14±0.42 | <0.001 | 1.35±0.23 |
| **Anterior** | 1.68±0.70 | 1.20±0.38 | <0.001 | 1.41±0.35 |
| **Lateral** | 1.57±0.65 | 1.27±0.54 | 0.002 | 1.25±0.18 |
| **Inferior** | 1.35±0.46 | 0.98±0.33 | <0.001 | 1.40±0.29 |
| **Septum** | 1.30±0.45 | 1.08±0.49 | 0.026 | 1.25±0.31 |
| **p (ANOVA)** | 0.054 | 0.082 | | 0.097 |

*p<0.001 hyperaemia versus rest for all values; † p<0.05 versus septum and lateral wall; ‡ p<0.05 versus septum and inferior wall; ¶ p=0.030 versus septum.

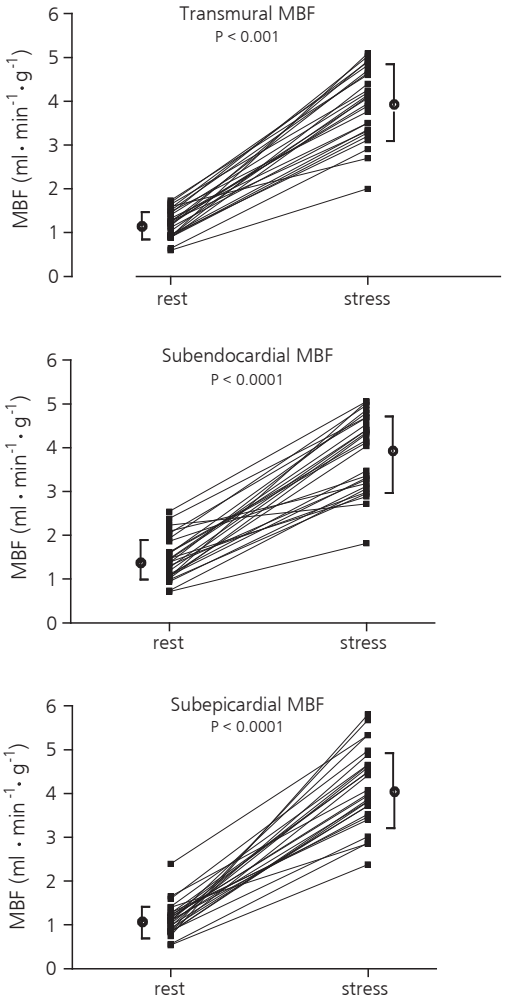



**FIGURE 2:** Transmural, subendocardial and subepicardial myocardial blood flow (MBF) during baseline and hyperaemic conditions. Note, subendocardial baseline MBF is higher than subepicardial (1.46 ± 0.49 versus 1.14 ± 0.42 ml·min$^{-1}$·g$^{-1}$, p<0.001). In contrast, hyperaemic MBF is lower in the subendocardium (3.88 ± 0.86 vs. 4.14 ± 0.88 ml·min$^{-1}$·g$^{-1}$, p<0.05).

| Hyperemia* | | | | CFR | | |
|---|---|---|---|---|---|---|
| **Endo** | **Epi** | **p** | **Endo / Epi** | **Endo** | **Epi** | **p** |
| 3.88±0.86 | 4.14±0.88 | 0.013 | 1.12±0.20 | 3.14±0.83 | 3.97±1.04 | <0.001 |
| 3.80±0.99 | 3.36±1.06† | 0.020 | 1.22±0.48¶ | 2.55±0.94 | 3.03±1.10‡ | 0.018 |
| 4.06±0.96 | 4.28±0.90 | 0.173 | 0.97±0.21 | 2.89±0.96 | 3.62±0.87 | <0.001 |
| 3.66±1.06 | 3.65±1.20 | 0.954 | 1.06±0.33 | 3.00±1.24 | 4.05±1.72 | <0.001 |
| 3.89±0.98 | 4.16±0.94 | 0.107 | 0.95±0.22 | 3.25±1.12 | 4.35±1.57 | <0.001 |
| 0.511 | 0.004 | | 0.011 | 0.118 | 0.004 | |

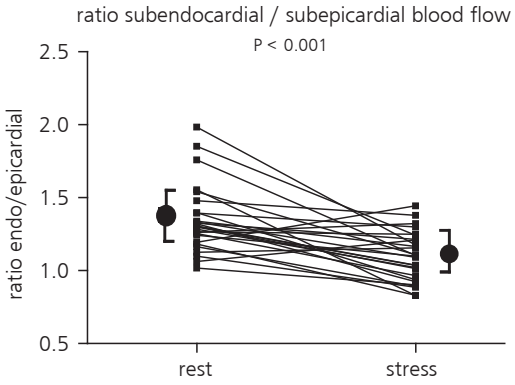



**FIGURE 3:** Endocardial-to-Epicardial myocardial blood flow ratio during baseline and hyperaemic conditions. During hyperaemia, there was a significant reduction in the endocardial-to epicardial ratio compared to rest (rest ratio 1.35 ± 0.23 vs. stress ratio 1.12 ± 0.20 p<0.001)

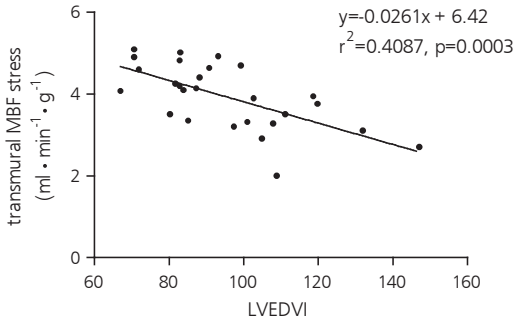
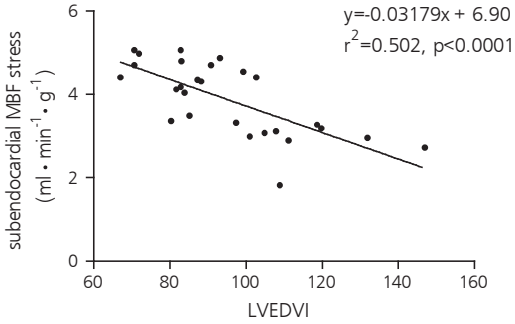
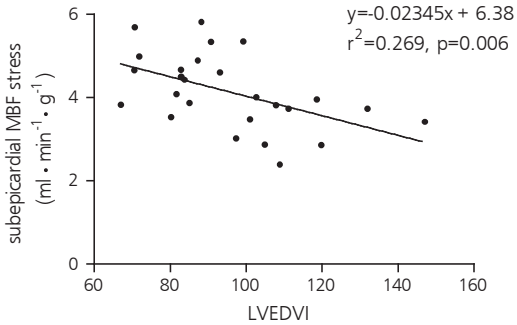



**FIGURE 4:** Hyperaemic transmural, subendocardial end subepicardial MBF in relation to left ventricular end-diastolic volume index (LVEDVI).



1.35 ± 0.23. During hyperaemia, there was a significant reduction in the endocardial-to epicardial ratio to 1.12 ± 0.20 ($p<0.001$), see Figure 3. Hyperemic MBF was 3.88 ± 0.86 in the subendocardium and 4.14 ± 0.88 $ml \cdot min^{-1} \cdot g^{-1}$ in the subepicardium ($p=0.013$). Hyperemic MBF increased to a greater extent at the subepicardial level compared with the subendocardial level, see Table 2. Baseline coronary vascular resistance (CVR) was 67±25 mmHg mL $min^{-1}$ and 87±31 mmHg mL $min^{-1}$ for the subendocardial and subepicardial layer, respectively. During hyperaemia CVR decreases to 22±7 mmHg mL $min^{-1}$ and 21±5 mmHg mL $min^{-1}$ respectively.

### Regional subendocardial vs. subepicardial MBF

Regional analysis for rest MBF revealed significant differences between the subendocardial and subepicardial layer for all segments (all $p<0.05$). During hyperaemia PET was able to distinguish perfusion differences between endocardium and epicardium only in the anterior segment ($p=0.020$) in the regional analysis.

There were no differences for subendocardial MBF between the four myocardial segments for resting ($p=0.054$) or hyperaemic ($p=0.511$) conditions, or CFR ($p=0.118$). Subepicardial MBF was distributed homogenously during rest ($p=0.082$). During hyperaemia, however, significant differences were observed ($p= 0.004$) where MBF was lower in the anterior segment as compared with the septum ($p=0.031$) and lateral wall ($p=0.009$). As a consequence, CFR in the anterior wall was also lower as compared with the septum ($p=0.004$) and inferior wall ($p=0.047$). No regional differences in the endo-to-epicardial ratio between segments were observed during rest ($p=0.097$), whereas during hyperaemia the ratio was higher in the anterior wall compared with the septum ($p=0.030$).

### Interrelations among PET and CMR parameters

Of the obtained PET and CMR parameters, only LVEDVI was (inversely) correlated to hyperaemic MBF (Figure 4). Of interest, the correlation was stronger at the subendocardial level as compared with the subepicardial level ($p<0.05$).

## DISCUSSION

The ability to distinguish subendocardial from subepicardial MBF using $H_2{}^{15}O$ PET has been investigated and validated in previous studies. (4, 11, 12, 13) These measurements, however, have been restricted to patients with left ventricular hypertrophy to overcome the issue of partial volume effects that are caused by the relatively limited resolution of PET. Only recently, Rimoldi et al. have demonstrated the feasibility to detect a transmural perfusion gradient using $H_2{}^{15}O$ PET in an animal experiment with pigs characterized by comparable cardiac dimensions as normal human hearts (~ 10 mm wall thickness)

(5). The current study extends to these observations and demonstrates that such a transmural perfusion gradient can similarly be detected in normal human subjects in a routine clinical setting with $H_2{}^{15}O$ PET.



The results show that MBF measurements in the subendocardial layer are approximately 35% higher than in the subepicardium during resting conditions. During hyperaemia, augmentation of perfusion is greater at the subepicardial level and the transmural perfusion gradient diminishes significantly, although average subendocardial MBF remains approximately 10% higher. The combination of these observations led to an overall lower CFR in the subendocardium. These results are in line with data obtained from previous animal experiments where perfusion was measured with microspheres. Under resting conditions, subendocardial MBF is indeed consistently higher as compared with the subepicardial layer, with endo-to-epi flow ratios varying from ~1.1 to 1.5. (5, 14-17) The latter observation is compatible with the fact that, under resting conditions, myocardial perfusion is autoregulated in response to varying metabolic demand. As loading conditions and, consequently, oxidative metabolism are greater in the subendocardial layer of the myocardium, resting perfusion will be augmented relative to the subepicardial layer. During hyperaemia, however, autoregulatory mechanisms are exhausted and myocardial perfusion is predominantly governed by intravascular (i.e. vascular resistance) and extravascular (i.e. diastolic perfusion time and wall stress) forces. (3, 18) As both intravascular and extravascular forces are increased in the subendocardium as compared with the subepicardial layer, a physiological transmural perfusion gradient drop can be observed during hyperaemia relative to resting conditions, as also documented in the current study. Pathophysiological conditions that are associated with elevated vascular resistance, irrespective of its origin, are characterized by a greater transmural gradient reduction and subendocardial flow frequently becomes even lower than subepicardial flow.(18) It is of interest to note that in the current study there was an inverse correlation between LVEDV and hyperaemic MBF. Although wall stress was not determined in these healthy subjects owing to the invasive nature of such measurements, according to Laplace's law LVEDV is one of the determinants of wall stress and may therefore represent a physiological relationship between end-diastolic wall stress and hyperaemic perfusion even within the relatively small range of end-diastolic volumes in normal subjects. (19) The fact that this relation was more apparent at the subendocardial level underscores this notion as wall stress progressively declines from the endo to epicardial level. Moreover, the relation between hyperaemic MBF and wall stress has been documented in previous studies, and subendocardial hyperaemic perfusion can (partially) be restored by lowering end-diastolic wall stress. (4, 6, 12, 14, 20, 21)

On average, transmural resting and hyperaemic MBF values, and hence CFR, were comparable to a previously reported large cohort of normal subjects studied with $H_2{}^{15}O$

PET.(22) Furthermore, some heterogeneity in both resting and hyperaemic MBF could be detected. Although these regional variations in perfusion may reflect a biological phenomenon, some technical consideratons must be taken into account. The model to quantify MBF contains an intrinsic correction for spillover from blood activity from both the left and right ventricular cavity, but not from adjacent tissue. This means that tissue surrounding the myocardium (such as the chest wall for the anterior segments, lung tissue for the lateral wall, and abdominal organs for the inferior wall) could influence perfusion values and lead to slight heterogeneity. Region definition in smaller areas of interest, such as with subendocardial en subepicardial flow measurements, will introduce more noise and potentially augment spillover artifacts from adjacent tissue. Moreover, spillover of activity between myocardial layers does also occur. Simulation models and *in vivo* studies have revealed that the latter will result in underestimation of the transmural gradient.(5, 11)

It is therefore expected that the observed perfusion differences between layers in the current study will actually be even more pronounced. Another issue concerns the model based corrections for partial volume.(23) This correction is warranted owing to the relatively limited resolution of PET relative to the normal myocardial wall thickness. This correction is fairly robust en reproducible for transmural flow measurement, but might pose limitations for smaller regions comprising only half of the myocardial wall. (24) Obviously, more studies are warranted pertaining reproducibility. Finally, but of paramount importance, there is the potential of cardiac and respiratory gating to further enhance the accuracy of subendocardial and subepicardial flow measurements. The current study was conducted without cardiac or respiratory gating as count statistics per gated frame would become insufficient for dynamic quantitative $H_2{}^{15}O$ perfusion imaging. Nonetheless, recent studies have clearly demonstrated that such gating sequences substantially improve spatial resolution.(25, 26) With the aid of list mode acquisition as well as time-of-flight sequences, future studies will certainly need to focus on the applicability of cardiac and respiratory gating to increase the spatial resolution in dynamic quantitative PET imaging to facilitate measurements of transmural myocardial perfusion gradients.(27, 28)

## Clinical implications

It seems that PET measurements of subendocardial/subepicardial flow ratio can be used as an index for subendocardial perfusion, using the subepicardial perfusion as a reference. Normal values of subendocardial perfusion and the subendocardial/subepicardial flow ratio are of potential clinical importance for identifying patients at risk of subendocardial ischaemia. In a recent study a decreased subendocardial/subepicardial flow ratio was found by PET for patients with hypertrophied hearts indicating microvascular dysfunction.(4) Coronary microvascular dysfunction is probably also the cause of the angina in a subgroup of cardiac syndrome X patients (angina-like

chest pain in the absence of obstructive CAD).(29, 30) Rosen et al reported however that no significant transmural MBF differences existed between cardiac syndrome X patients and controls using $^{15}$O-labeled water PET.(31) However, this does not exclude subendocardial ischaemia in this group of patients. (32, 33) Further studies using PET may reveal possible subendocardial ischemia in patients with cardiac syndrome X. Hence quantification of regional myocardial blood flow may be clinically useful not only for assessing the extent and severity of coronary vascular disease, but also to detect and measure impairments in microcirculatory function in non-coronary cardiac disease. The prognostic significance of transmural microcirculatory dysfunction in the absence of CAD however remains to be assessed.

# CONCLUSIONS

This study demonstrates the feasibility of using $^{15}$O-labeled water positron emission tomography (PET) to measure myocardial blood flow in both the subendocardial and subepicardial layers of a left ventricle of normal thickness. This PET technique may prove useful in evaluating patients with signs of ischaemia due to microvascular dysfunction.

# ACKNOWLEDGMENTS

We thank Dr R.J.H. Wanhill PhD for his critical review and editing of the manuscript.

# REFERENCE LIST

1. Algranati D, Kassab GS, Lanir Y. Why is the Subendocardium more Vulnerable to Ischemia? A New Paradigm. *Am J Physiol Heart Circ Physiol* 2010 Dec 17.
2. Camici PG, Rimoldi OE. The clinical value of myocardial blood flow measurement. *J Nucl Med* 2009 Jul;50(7):1076-1087.
3. Knaapen P, Camici PG, Marques KM, Nijveldt R, Bax JJ, Westerhof N, et al. Coronary microvascular resistance: methods for its quantification in humans. *Basic Res Cardiol* 2009 Sep;104(5):485-498.
4. Knaapen P, Germans T, Camici PG, Rimoldi OE, ten Cate FJ, ten Berg JM, et al. Determinants of coronary microvascular dysfunction in symptomatic hypertrophic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2008 Feb;294(2):H986-H993.
5. Rimoldi O, Schafers KP, Boellaard R, Turkheimer F, Stegger L, Law MP, et al. Quantification of subendocardial and subepicardial blood flow using 15O-labeled water and PET: experimental validation. *J Nucl Med* 2006 Jan;47(1):163-172.
6. Knaapen P, van Campen LM, de Cock CC, Gotte MJ, Visser CA, Lammertsma AA, et al. Effects of cardiac resynchronization therapy on myocardial perfusion reserve. *Circulation* 2004 Aug 10;110(6):646-651.
7. Hofman HA, Knaapen P, Boellaard R, Bondarenko O, Gotte MJ, van Dockum WG, et al. Measurement of left ventricular volumes and function with O-15-labeled carbon monoxide gated positron emission tomography: comparison with magnetic resonance imaging. *J Nucl Cardiol* 2005 Nov;12(6):639-644.
8. Boellaard R, Knaapen P, Rijbroek A, Luurtsema GJ, Lammertsma AA. Evaluation of basis function and linear least squares methods for generating parametric blood flow images using 15O-water and Positron Emission Tomography. *Mol Imaging Biol* 2005 Jul;7(4):273-285.
9. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *J Nucl Cardiol* 2002 Mar;9(2):240-245.
10. Knaapen P, Boellaard R, Gotte MJ, Dijkmans PA, van Campen LM, de Cock CC, et al. Perfusable tissue index as a potential marker of fibrosis in patients with idiopathic dilated cardiomyopathy. *J Nucl Med* 2004 Aug;45(8):1299-1304.
11. Choudhury L, Elliott P, Rimoldi O, Ryan M, Lammertsma AA, Boyd H, et al. Transmural myocardial blood flow distribution in hypertrophic cardiomyopathy and effect of treatment. *Basic Res Cardiol* 1999 Feb;94(1):49-59.
12. Rajappan K, Rimoldi OE, Dutka DP, Ariff B, Pennell DJ, Sheridan DJ, et al. Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. *Circulation* 2002 Jan 29;105(4):470-476.
13. Timmer SA, Knaapen P, Lubberink M, Lammerstma AA, Germans T, Dijkmans PA, et al. Effects of Alcohol Septal Ablation on Coronary Microvascular Function and Myocardial Energetics in Hypertrophic Obstructive Cardiomyopathy. 2010.
14. Hittinger L, Mirsky I, Shen YT, Patrick TA, Bishop SP, Vatner SF. Hemodynamic mechanisms responsible for reduced subendocardial coronary reserve in dogs with severe left ventricular hypertrophy. *Circulation* 1995 Aug 15;92(4):978-986.
15. Duncker DJ, Ishibashi Y, Bache RJ. Effect of treadmill exercise on transmural distribution of blood flow in hypertrophied left ventricle. *Am J Physiol* 1998 Oct;275(4 Pt 2):H1274-H1282.

16. Pagny JY, Peronnet F, Beliveau L, Sestier F, Nadeau R. Systemic and regional blood flows during graded treadmill exercise in dogs. *J Physiol (Paris)* 1986;81(5):368-373.

17. White FC, Roth DM, Bloor CM. Coronary collateral reserve during exercise induced ischemia in swine. *Basic Res Cardiol* 1989 Jan;84(1):42-54.

18. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiol Rev* 2008 Jul;88(3):1009-1086.

19. Gaasch WH. Left ventricular radius to wall thickness ratio. *Am J Cardiol* 1979 Jun;43(6):1189-1194.

20. Knaapen P, Gotte MJ, Paulus WJ, Zwanenburg JJ, Dijkmans PA, Boellaard R, et al. Does myocardial fibrosis hinder contractile function and perfusion in idiopathic dilated cardiomyopathy? PET and MR imaging study. *Radiology* 2006 Aug;240(2):380-388.

21. Rajappan K, Rimoldi OE, Camici PG, Bellenger NG, Pennell DJ, Sheridan DJ. Functional changes in coronary microcirculation after valve replacement in patients with aortic stenosis. *Circulation* 2003 Jul 1;107(25):3170-3175.

22. Chareonthaitawee P, Kaufmann PA, Rimoldi O, Camici PG. Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. *Cardiovasc Res* 2001 Apr;50(1):151-161.

23. Iida H, Kanno I, Takahashi A, Miura S, Murakami M, Takahashi K, et al. Measurement of absolute myocardial blood flow with H215O and dynamic positron-emission tomography. Strategy for quantification in relation to the partial-volume effect. *Circulation* 1988 Jul;78(1):104-115.

24. Kaufmann PA, Gnecchi-Ruscone T, Yap JT, Rimoldi O, Camici PG. Assessment of the reproducibility of baseline and hyperemic myocardial blood flow measurements with 15O-labeled water and PET. *J Nucl Med* 1999 Nov;40(11):1848-1856.

25. Kokki T, Sipila HT, Teras M, Noponen T, Durand-Schaefer N, Klen R, et al. Dual gated PET/CT imaging of small targets of the heart: method description and testing with a dynamic heart phantom. *J Nucl Cardiol* 2010 Jan;17(1):71-84.

26. Teras M, Kokki T, Durand-Schaefer N, Noponen T, Pietila M, Kiss J, et al. Dual-gated cardiac PET-clinical feasibility study. *Eur J Nucl Med Mol Imaging* 2010 Mar;37(3):505-516.

27. Buther F, Dawood M, Stegger L, Wubbeling F, Schafers M, Schober O, et al. List mode-driven cardiac and respiratory gating in PET. *J Nucl Med* 2009 May;50(5):674-681.

28. Mullani NA. Additional gains with time-of-flight PET at high counting rates: lessons learned from early time-of-flight PET systems. *J Nucl Med* 2010 Sep;51(9):1491-1493.

29. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med* 2007 Feb 22;356(8):830-840.

30. Vermeltfoort IA, Bondarenko O, Raijmakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, et al. Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study. *Eur Heart J* 2007 Jul;28(13):1554-1558.

31. Rosen SD, Uren NG, Kaski JC, Tousoulis D, Davies GJ, Camici PG. Coronary vasodilator reserve, pain perception, and sex in patients with syndrome X. *Circulation* 1994 Jul;90(1):50-60.

32. Lanza GA, Buffon A, Sestito A, Natale L, Sgueglia GA, Galiuto L, et al. Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. *J Am Coll Cardiol* 2008 Jan 29;51(4):466-472.

33. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002 Jun 20;346(25):1948-1953.

# Chapter 8

submitted

# Long-term prognosis of patients with cardiac syndrome X; review

I.A.C. Vermeltfoort[1] MD , G.J.J. Teule[1] PhD, A.B van Dijk[1] MD,
H.J. Muntinga[2] PhD, P.G.H.M. Raijmakers PhD[3]

1 Department of Nuclear Medicine, Verbeeten Institute, Postbus 90120, 5000 LA Tilburg, The Netherlands
2 Department of Cardiology, Tweesteden hospital, Dr Deelenlaan 5, 5042 AD Tilburg, The Netherlands
3 Department of Nuclear Medicine & PET Research, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands

# ABSTRACT

**Aims:** Follow-up studies of patients with cardiac syndrome X (CSX) generally report good prognosis. However, some recent studies report an adverse outcome for women.



**Methods and Results:** Structured literature search and meta-analysis for studies regarding prognosis of cardiac syndrome X patients.
We identified 85 studies, ultimately selecting 16 for inclusion. Meta-analysis yielded a pooled major cardiac event percentage of 1.5% per 5 years and a pooled vascular event percentage of 4.8% per 5 years (n=16 studies, n=1694 patients). 14 studies reported upon the recurrence rate of angina pectoris: the pooled percentage of angina recurrence is 55% (n= 1336 patients). Finally, the pooled percentage of female patients is 49% (n= 13 studies, n=1294 patients).

**Conclusion:** The present review of recent archival literature demonstrates a pooled proportion of female patients of 49%. This argues against the generally accepted opinion and statement that CSX occurs typically or preferentially in women. The overall major cardiac event rate is 1.5% per 5 years. Although this is an excellent prognosis for CSX patients, the quality of life is impaired because of the high recurrence rate of angina pectoris (55%).

# INTRODUCTION

Cardiac syndrome X (CSX) is the syndrome of angina pectoris during a positive stress test despite a normal coronary arteriogram. CSX is an important clinical entity(1-19). About 3-11% of patients undergoing coronary angiography because of typical chest pain have normal coronary arteries and qualify for the definition of CSX(19).

In overviews and textbooks it is often stated that (pre-menopausal) women are especially prone to developing CSX. In fact, some studies concern only female patient populations, while others vary considerably in the proportion of women examined and tested. This situation needs reassessment.

Follow-up studies of patients with CSX generally report good prognosis(7, 9). However, a recent study reported an adverse cardiovascular outcome for women with chest pain and normal coronary arteries (6).

Therefore, the present paper reviews the recent literature on CSX to clarify the question of gender preference and discuss in detail the long-term prognosis.

# METHODS OF IDENTIFYING AND SELECTING THE LITERATURE

A review and meta-analysis of the literature was conducted with a comprehensive search of the PUBMED database to identify clinical studies on CSX that considered prognosis. The prognosis of CSX patients was derived from the cardiac event rate per year for each study and the recurrence rate of angina (when included in the studies). Furthermore, the gender distribution of the patient populations was considered.

Studies were eligible for review if they met the following standardized inclusion criteria (20-22): Full length articles; studies including CSX or patients with angina and normal coronary arteries; minimum number of 10 patients; studies presenting follow-up data of more than 2 years; and publication dates between April 1985 and February 2010.

The criteria for excluding studies were: metabolic syndrome X; studies including patients with near-normal coronary angiography (CAG) results; and studies of patients with myocardial infarction and/or cardiomyopathy were excluded.

In detail, the PubMed database was used to identify papers in which definitions and prognosis for CSX are described via the following terms:

'((Prognosis or follow up) AND ((((cardiac syndrome x OR (angina pectoris AND normal coronary arteries) OR microvascular angina)) AND (((“microvascular angina”[TIAB] NOT Medline[SB]) OR “microvascular angina”[MeSH Terms] OR cardiac syndrome x[Text Word]))) AND ((“syndrome x”[All] OR (((angina pectoris) OR (chest pain)) AND normal AND (coronary[tw] OR angiogra*[tw])) OR (microvascular angina)))) AND

((Humans[Mesh]) AND (English[lang]) AND (adult[MeSH]))’; with limits set to English language and humans.

The search strategy identified 85 studies from PUBMED. These became the source population for this review. The titles were screened for eligibility by one of the reviewers (I.V.), followed by two reviewers (I.V. and P.R.) independently assessing the abstracts by consensus. In this initial screening a total of 23 articles were excluded because of:



a Metabolic syndrome X, myocardial infarction and tako-tsubo cardiomyopathy (14 references).
b Non-performance of coronary angiography (2 references).
c Studies with coronary spasm (3), case report (1), antiphospholipid syndrome (1) and non-obstructive coronary artery disease (2) in the title.

62 papers remained. The titles of these studies contained cardiac syndrome X (44 papers), normal coronary arteries (14 papers) and microvascular angina (4 papers).

The full texts of all 62 papers were retrieved for further selection, notably as to whether they considered prognosis. Only 17 included prognosis, but checking the references from all 17 resulted in another 4 papers being selected (1, 6, 12, 14). Of these remaining

**TABLE 1** cardiac syndrome X

| First author | year | No | Average Age (yr) | % Men | Average Follow-up (yr) | Coronary event | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Death | Myocardial Infarction | CAD |
| Bugiardini [1] | 2004 | 42 | 51.6±8.8 | 0 | 10.3 | 1 | 0 | 13 |
| Chauhan [2] | 1993 | 41 | 46±4 | 39 | 2.9 | 0 | 0 | 0 |
| Delcour [3] | 2009 | 48 | 60.9±12 | 100 | 7.4 | 0 | 1 | 5 |
| Foussas [4] | 1998 | 160 | 50.0 | 69 | 2.5 | 1 | 2 | 0 |
| Fragasso [5] | 2009 | 34 | 56 | 20 | 14 ± 2 | 0 | 2 | 2 |
| Gulati [6] | 2009 | 318 | 53.6±10.4 | 0 | 5.2 | 5 | 3 | 0 |
| Kaski [7] | 1995 | 99 | 48.5±8 | 21 | 7±4 | 0 | 0 | 0 |
| Lamendola [8] | 2008 | 155 | 58.9±10 | 26 | 11.4±6.5 | 0 | 0 | 3 |
| Leu [9] | 2005 | 92 | 63.9±10.5 | 78 | 2.6±1.2 | 0 | 0 | 0 |
| Lichtlen [10] | 1995 | 176 | 48.3 | 65 | 12.4 | 2 | 4 | 8 |
| Radice [11] | 1995 | 30 | 51±6 | 27 | 12.3±3.5 | 0 | 0 | 0 |
| Scholz [12] | 2002 | 173 | 54±7.8 | 59 | 12.0±2.9 | 10 | 0 | 6 |
| Shintani [13] | 2003 | 43 | 55±8 | 7 | 6.4±3.8 | 0 | 0 | 0 |
| Sullivan [14] | 1994 | 138 | 50.0 | 55 | 2.4 | 0 | 1 | 0 |
| Sun [15] | 2001 | 59 | 61±5 | 88 | 7.1±1.4 | 0 | 1 | 0 |
| Suzuki [16] | 2002 | 86 | 59 ± 9 | 41 | 7.2 ± 3.4 | 0 | 0 | 0 |

- = non-available

21 papers, 9 described CSX, 11 described AP and normal coronary arteries (NCA), and 1 described microvascular angina.

Finally, the 21 papers were independently surveyed by two authors (IV and PR) with respect to the definition of CSX and prognosis. This resulted in 5 papers being excluded as follows: an NCA study (23) also included minimal lesions of the coronary arteries with a reduction in diameter of less than 50%; one turned out to be only a letter(24); 2 intervention studies did not report cardiac events (25, 26); and another appeared to be an intervention study of only 7 patients(27), whereas the agreed minimum number of patients for our review was 10.

This survey left 16 papers for the present review. These papers covered a total of 1694 patients. For each paper we extracted the number of patients; cardiovascular event rates; percentage of female/male patients (for studies including both female and male patients); and the percentage of patients with recurrent chest pain. In more detail:

1 Major adverse cardiac event (MACE) rates included cardiac death, myocardial infarction and revascularization as defined by the most recent ACC/AHA guidelines 2010 and other studies(28-30).

| % Rec chest pain | % Repeat CAG | |
|---|---|---|
| 31 | - | |
| 64 | - | |
| - | - | 6 CVA |
| 59 | - | |
| 65 | - | 1 LV dysfunction |
| - | - | 8 CVA. 10 LV dysfunction |
| 89 | - | 1 LV dyfunction |
| 48 | 21 | |
| 13 | 9 | 1 LV dysfunction 3 CVA |
| 81 | 12 | |
| 33 | 27 | |
| 34 | - | |
| 44 | - | |
| 70 | - | |
| 76 | - | 10 LV dysfunction |
| 35 | 2 | |

2 The vascular events included myocardial infarction, cardiac death, development of CAD, heart failure, and the occurrence of cerebrovascular events (http://www.framinghamheartstudy.org/risk/gencardio.html).
3 Since some of the studies had different follow-up periods, we normalized the event rates to those per 5 years.
4 Before calculation of the pooled estimates of major cardiac event rates, cardiovascular event rates, chest pain recurrence rates and gender distribution, the heterogeneity of these values was tested using calculation of $I^2$ and the Chi-square test with k-1 degrees of freedom (k=number of studies). $I^2$ reflects the percentage of variation between the studies attributable to heterogeneity rather than chance. $I^2$ ranges from 0% to 100%, and values higher than 50% reflect considerable heterogeneity across the studies. The effects of follow-up period, gender distribution and mean age of the populations upon the cardiovascular event rates were studied using regression analysis: P values < 0.05 were considered to be significant.

# RESULTS

Table 1 lists the 16 studies included in this review. Note that (a) 2 studies did not report the frequency of chest pain(3, 6), (b) the follow-up period varied widely, from 2.4 years to 14 years, and (c) 3 studies did not have male and female patients(1, 3, 6).

CSX prognosis

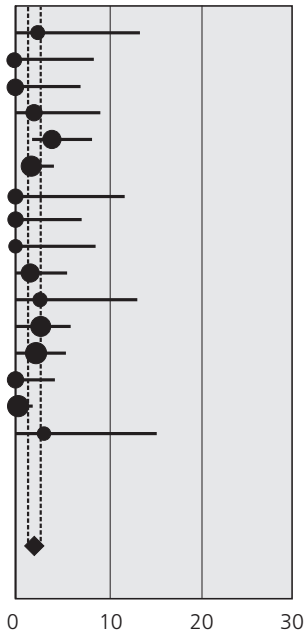
The three most important results relating to prognosis are:

1 The major cardiac event rate varied from 0 – 3.8% per 5 years, with a pooled value of 1.5% per 5 years (95% CI: 1 – 2.2%, n = 1694 patients), see figure 1. There was no significant heterogeneity between included studies regarding the major cardiac event rate ($I^2$ = 37%, Chi-square 23.7, p = 0.074). The estimated annual major cardiac event rate was 0.3%. This includes myocardial infarction, revascularization and cardiovascular death, see table 1.
2 The general cardiovascular event rate varied from 0 – 16.7% per 5 years, with a pooled value of 4.8% for 5 years (95% CI: 3.8 – 5.9%). However, there was significant heterogeneity ($I^2$ = 79%, Chi-square 71.7, p < 0.001), see figure 2.
3 There were 14 studies with 1336 patients for analysis of recurrent chest pain. The recurrence rate varied between 13.2% to 89.9% for the different study populations, with a pooled value of 55% (95% CI: 53 – 58% , n = 1336 patients). There was significant heterogeneity (Chi-square 274.9, p < 0.001), see figure 3.

The remaining results are:

4 The major cardiac event rate was not related to the length of follow-up ($R^2$ = 0.0043), mean age ($R^2$ = 0.000006) and percentage of female patients ($R^2$ = 0.0268).

Major cardiac events rate

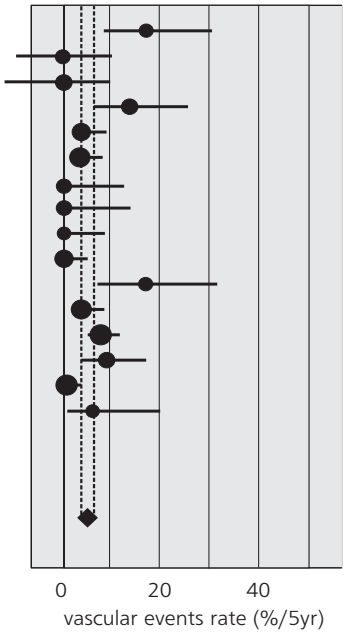



Author:

Delcour
Shintani
Suzuki
Sun
Foussas
Lichtlen
Radice
Kaski
Chauhan
Sullivan
Bugiardini
Scholz
Gulati
Leu
Lamendola
Fragrasso

Pooled vascular event rate: 1.5% (1.0 - 2.2%)

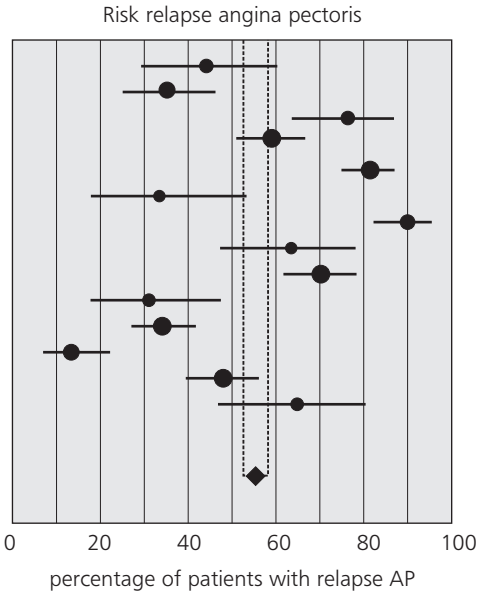
Vascular events




Author:

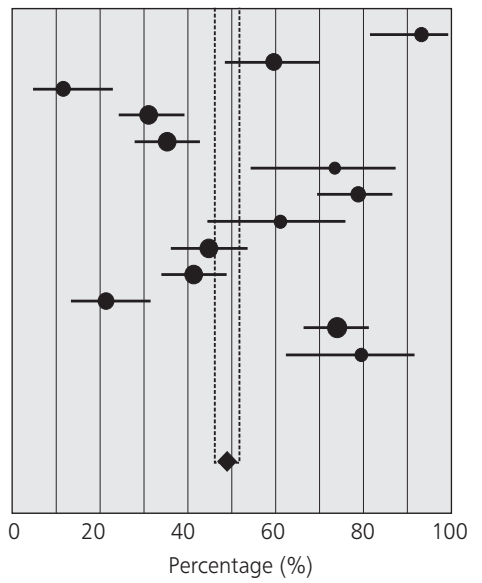
Delcour
Shintani
Suzuki
Sun
Foussas
Lichtlen
Radice
Kaski
Chauhan
Sullivan
Bugiardini
Scholz
Gulati
Leu
Lamendola
Fragrasso

Pooled vascular event rate: 4.8% (3.8 - 5.9%)




| | | |
|---|---|---|
| Shintani | 0,44 | (0,29 - 0,60) |
| Suzuki | 0,35 | (0,25 - 0,46) |
| Sun | 0,76 | (0,63 - 0,86) |
| Foussas | 0,59 | (0,51 - 0,66) |
| Lichtlen | 0,81 | (0,75 - 0,87) |
| Radice | 0,33 | (0,17 - 0,53) |
| Kaski | 0,90 | (0,82 - 0,95) |
| Chauhan | 0,63 | (0,47 - 0,78) |
| Sullivan | 0,70 | (0,62 - 0,78) |
| Bugiardini | 0,31 | (0,18 - 0,47) |
| Scholz | 0,34 | (0,27 - 0,42) |
| Leu | 0,13 | (0,07 - 0,22) |
| Lamendola | 0,48 | (0,40 - 0,56) |
| Fragrasso | 0,65 | (0,46 - 0,80) |

Pooled percentage = 55% (53 - 58%)




Shintani
Suzuki
Sun
Foussas
Lichtlen
Radice
Kaski
Chauhan
Sullivan
Scholz
Leu
Lamendola
Fragrasso

Pooled percentage = 49% (46 - 52%)

(a) Follow-up $R^2 = 0.0043$, $y = 0.0002*x + 0.011$, (b) Age $R^2 = 6.10^{-6}$, $y = 5.10\text{-}6*x + 0.0123$), (c) Female percentage $R^2 = 0.0268$, $y = 6.10\text{-}5*x+0.016$).

5 The total vascular cardiac event rate per study was not related to the length of follow-up ($R^2 = 0.0011$), mean age ( $R^2 = 0.238$) and percentage of female patients ($R^2 = 0.063$).

(a) Follow up $R^2 = 0.0011$, $y = 0.0005*x + 0.0484$, (b) Age $R^2$ 0.2376, $y = 0.00042*x + 0.1793$, (c) Female percentage $R^2 = 0.063$, $y = 0.0004 *x + 0.0758$).

6 There were 13 studies available for possible gender differences. The percentage of female patients ranged from 11.9% to 93.0%, with a pooled percentage of 49.2% (95% CI: 46.5% – 52.0%), n = 1294 patients), see figure 4.



# DISCUSSION

## CSX gender distribution

The proportion of women in the 16 studies included in this review varied considerably, ranging from 0.12 to 1.0, with a pooled estimate of 0.49. Thus we conclude that there is no significant gender preference with respect to CSX.

It is generally accepted (e.g. in authoritative textbooks) that the majority of CSX patients are women. Some authors, as in the WISE study, have even suggested that CSX is a women's disease(6). The systematical review data do not support the assumption or suggestion that CSX is a women's disease, since 51% of the population was male. Potential pathophysiological explanations based on gender, such as estrogen depletion, obviously apply to only part of the population(31, 32).

A wealth of recent evidence from patients referred for coronary angiography notes more frequent non-obstructive CAD in women than in men. Women with extensive CAD have a higher mortality than men with the same condition. Moreover, the extent of non-obstructive CAD, as measured by coronary computed tomographic angiography, predicts mortality in women but not in men. This led Shaw to hypothesize that a gender-specific pathobiological process, responsible for atherosclerotic disease, could explain the difference(33). Be that as it may, this difference is important for the CSX gender discussion: there could be two different types of CSX, warranting different diagnostic and therapeutic strategies for each gender. This possibility requires further investigation.

## Overall cardiac event rates

This systematic review shows that the CSX prognosis in terms of the overall cardiac event rate is excellent, with a risk upon myocardial infarction or cardiovascular death of 1.5% per 5 years. The Framingham Heart Study reported annual hard (death, myocardial infarction) coronary event rates of 1.2% (men < 65 years); 2.7% (men > 65 years); 0.5% (women < 65 years); and 1.6% (women > 65 years). These rates are all higher than the major adverse cardiac event (MACE) rate for CSX patients determined from our systematic review.

The lower cardiac event rates for CSX patients suggest that they may benefit from protective factors against coronary macrovascular disease. These factors could be (a) cardioprotective medication, (b) a healthier lifestyle to avoid angina and myocardial infarction, e.g. becoming non-smokers, and (c) another biological mechanism. A possible example of the latter is the observation that platelet reactivity decreases after stress in patients with CSX, in contrast to patients with coronary artery disease (CAD)(34, 35). On the other hand, the better prognosis of CSX patients compared to the general population may result from a selection process. CSX patients all have, *by definition*, normal coronary arteries, which is not necessarily the case in the general population. The difference in prevalence of coronary atherosclerosis between CSX patients and the general population may explain the difference in cardiac event rates.

The notion of the benign nature of CSX has been challenged by reports of a high risk of future cardiac events in patients with angina and normal coronary arteries(1, 36, 37). A recent study, named the Women's Ischaemia Syndrome Evaluation (WISE) study involved 540 symptomatic women referred for coronary angiography and followed up for a mean of 5.2 years. The control group was asymptomatic, and consisted of community-based age- and race-matched women with no history of heart disease, and who were followed up for 10 years.

The WISE study showed a cardiovascular event rate of 7.9% per 5 years for women with angina and normal coronary arteries (CSX), compared to 2.4% per 5 years for the asymptomatic control group(6). The WISE study CSX event rate lies outside the 95% confidence interval of 3.8% – 5.9% per 5 years that we found from our reviewed studies. However, the rate of cardiovascular death was not significantly different between de CSX women and the control (asymptomatic) women in the WISE study. The increased cardiovascular event rate in symptomatic women with normal coronary arteries was largely accounted for by an increased incidence of hospitalisation for heart failure and stroke. It remains unexplained why the incidence of heart failure and stroke are increased in this specific population, although microvascular dysfunction might precede macrovascular atherosclerosis.

## CSX and non-obstructive CAD cardiac event rates

It is important to distinguish between CSX, with normal coronary arteries, and non-obstructive CAD (19). The cardiac event rate for CSX patients is significantly better than that for patients with angina and non-obstructive CAD. This is illustrated by Sicari (38), who reported that a subgroup of patients with angina and non-obstructive CAD (incorrectly identified as CSX), and with positive dipyridamole echocardiography tests, had a survival rate of only 76% after 7.1 years follow-up.

Five year cardiac event rates for cardiovascular events were significantly different for three subgroups in the WISE study: 16% per 5 years for women with angina and non-

obstructive CAD (stenosis <50%); 7.9% per 5 years for women with angina and normal coronary arteries (CSX); and 2.4% per 5 years for the asymptomatic control group (P ≤ 0.002)(6). Hence, in this large study a higher incidence of events in symptomatic women with non-obstructed CAD was found compared with patients with symptoms and normal coronary arteries.

## CSX and coronary microvascular dysfunction (CMVD)

Lanza recently proposed to rename CSX as stable primary coronary microvascular dysfunction (CMVD)(39). This proposal was made on the premise that abnormalities in the coronary microcirculation are the probable cause of CSX ischaemia and angina. However, Herzog obtained contemporary positron emission tomography (PET) data that suggest an increased cardiac event rate for patients with microvascular dysfunction, irrespective of abnormalities in the epicardial coronary arteries(40). (Note: this study was not included in our literature review because CAGs were not performed.)

In the study by Herzog the patients with a reduced flow reserve, defined as a CFR < 2.0, had a higher annual cardiac event rate and a higher risk of cardiac death, and this included patients with a normal perfusion PET (40). Specifically, a subgroup of patients with normal perfusion but impaired CFR had a significantly higher major annual cardiac event rate (6.25%) compared to patients with a normal CFR (1.4%). Also, the annual cardiac death rate was higher: 3.1% for patients with normal perfusion but impaired CFR, compared to 0.5% for patients with normal CFR. Thus it is possible for patients with a normal perfusion, who therefore are unlikely to have epicardial coronary obstructive disease, to already have a reduced CFR, and that this is associated with a higher cardiac event rate or higher risk of cardiac death. The reduced CFR was most likely caused by microvascular or endothelial dysfunction(40). Therefore one should be cautious about equating CSX (which has a generally good prognosis) with coronary microvascular dysfunction,

Limitations to the significance of the study by Herzog are (a) the relatively small number of patients in the subgroup with normal perfusion and impaired CFR (n = 32), and (b) that after 10 years follow-up the impaired CFR could not predict any cardiac event in this subgroup(40). Hence larger prospective studies are needed. Be that as it may, we may conclude that a distinguishing diagnosis between CSX and CMVD requires evaluation of the distal compartment (intramural arterioles) as well as the proximal compartment (the large epicardial coronary arteries).

## Recurring chest pain

As stated earlier, recurrence of chest pain occurred in an average of 55% of the CSX cases included in our systematic review. In the study by Lantinga, 85% had at least weekly

episodes of chest pain up to 1 year after the angiograms, with the pain unchanged or even worse; and 33% underwent at least one more coronary angiography(41).

The most important therapy consists of reassurance, risk factor modification, and symptom relief (ACC/AHA guidelines 2002, www.acc.org/qualityandscience/clinical/statements.htm). There are conflicting data about the exact cause of chest pain in patients with CSX, There is evidence for ischaemia (17, 42), and alternatively, psychological factors like an increased anxiety may play a role in CSX (18). The number of pain episodes can be reduced by beta-blockers, calcium antagonists, nitrates and imipramine, which is particularly successful(43). Similar success has been claimed for estrogen replacement therapy(31, 32). In a patient with coronary spasms we found an increase of the myocardial blood flow and decrease of symptoms using bosentan, an endothelin receptor antagonist(44). However, the therapeutic measures remain largely empirical, and the symptoms persist in many patients.



# LIMITATIONS

Systematic reviews are hampered by publication bias, i.e., the preferential publication of studies with significant positive results rather than those with negative results. However, in studies regarding prognosis and survival this phenomenon is probably less frequent compared to studies evaluating therapeutic strategies.

Another potential problem is that clinical prognostic studies are almost inevitably different in their length of follow-up, which can affect the study results because longer follow-up periods might yield more exact prognostic figures. However, in our review we found no relation between the length of follow-up and event rates.

There are possible limitations owing to varying inclusion criteria for the different studies. These variations can cause heterogeneous meta-analysis results. For example, we found in earlier work that there were more than 50 different criteria (nine different inclusion criteria and forty-three different exclusion criteria) for CSX, resulting in a varying reported incidence of CSX(19). Also, the heterogeneity of the different study populations may have contributed to the heterogeneity that we found with respect to the prognoses from the studies.

On the other hand, the advantages of reviews and meta-analyses are an increase in statistical power, the ability to assess sources of heterogeneity, and the provision of overall estimates of prognostic variables.

# CONCLUSIONS

The present review of recent archival literature on CSX demonstrates no clear gender differences for the incidence of CSX, in contrast to the general assumption or suggestion that CSX is a women's disease. This systematic review found an overall major adverse cardiac event rate of 1.5% per 5 years. This represents a better prognosis compared to the general population. However, angina pectoris in CSX is recurrent and persistent in 55% of the patients, and significantly impairs the quality of life.

Whether CSX patients benefit from protective factors against acute coronary events is a challenging issue that should be addressed in future studies. The possibility that there are two types of CSX, related to gender, should also be investigated.

# ACKNOWLEDGEMENTS

We thank Dr R.J.H. Wanhill for his critical review and editing of the manuscript.
**Conflict of interest:** none declared

## Reference List




1. Bugiardini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease: a study of women with chest pain and normal coronary angiograms. *Circulation* 2004 Jun 1;109(21):2518-2523.
2. Chauhan A, Mullins PA, Thuraisingham SI, Petch MC, Schofield PM. Clinical presentation and functional prognosis in syndrome X. *Br Heart J* 1993 Oct;70(4):346-351.
3. Delcour KS, Khaja A, Chockalingam A, Kuppuswamy S, Dresser T. Outcomes in patients with abnormal myocardial perfusion imaging and normal coronary angiogram. *Angiology* 2009 Jun;60(3):318-321.
4. Foussas SG, Adamopoulou EN, Kafaltis NA, Fakiolas C, Olympios C, Pisimissis E, et al. Clinical characteristics and follow-up of patients with chest pain and normal coronary arteries. *Angiology* 1998 May;49(5):349-354.
5. Fragasso G, Chierchia SL, Arioli F, Carandente O, Gerosa S, Carlino M, et al. Coronary slow-flow causing transient myocardial hypoperfusion in patients with cardiac syndrome X: long-term clinical and functional prognosis. *Int J Cardiol* 2009 Oct 2;137(2):137-144.
6. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 2009 May 11;169(9):843-850.
7. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. *J Am Coll Cardiol* 1995 Mar 15;25(4):807-814.
8. Lamendola P, Lanza GA, Spinelli A, Sgueglia GA, Di MA, Barone L, et al. Long-term prognosis of patients with cardiac syndrome X. *Int J Cardiol* 2010 Apr 15;140(2):197-199.
9. Leu HB, Lin CP, Lin WT, Wu TC, Lin SJ, Chen JW. Circulating mononuclear superoxide production and inflammatory markers for long-term prognosis in patients with cardiac syndrome X. *Free Radic Biol Med* 2006 Mar 15;40(6):983-991.
10. Lichtlen PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. *J Am Coll Cardiol* 1995 Apr;25(5):1013-1018.
11. Radice M, Giudici V, Marinelli G. Long-term follow-up in patients with positive exercise test and angiographically normal coronary arteries (syndrome X). *Am J Cardiol* 1995 Mar 15;75(8):620-621.
12. Scholz M, Wegener K, Unverdorben M, Klepzig H. [Long-term outcome in patients with angina-like chest pain and normal coronary angiograms]. *Herz* 2003 Aug;28(5):413-420.
13. Shintani S, Nishiyama Y, Yamamoto K, Koga Y. Different long-term course between chest pain and exercise-induced ST depression in syndrome X. *Jpn Heart J* 2003 Jul;44(4):471-479.
14. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. *BMJ* 1994 Apr 2;308(6933):883-886.
15. Sun SS, Huang JL, Tsai SC, Ho YJ, Kao CH. The higher likelihood of developing cardiomegaly during follow-up in patients with syndrome X and abnormal thallium-201 myocardial perfusion SPECT. *Int J Cardiovasc Imaging* 2001 Aug;17(4):271-278.
16. Suzuki H, Matsubara H, Koba S, Murakami M, Takeyama Y, Katagiri T. Clinical characteristics and follow-up in patients with microvascular angina. *Circ J* 2002 Jul;66(7):691-695.

17. Vermeltfoort IA, Bondarenko O, Raijmakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, et al. Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study. *Eur Heart J* 2007 Jul;28(13):1554-1558.

18. Vermeltfoort IA, Raijmakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, Teule GJ. Association between anxiety disorder and the extent of ischemia observed in cardiac syndrome X. *J Nucl Cardiol* 2009 May;16(3):405-410.

19. Vermeltfoort IA, Raijmakers PG, Riphagen II, Odekerken DA, Kuijper AF, Zwijnenburg A, et al. Definitions and incidence of cardiac syndrome X: review and analysis of clinical data. *Clin Res Cardiol* 2010 Aug;99(8):475-481.

20. Mijnhout GS, Riphagen II, Hoekstra OS. Update of the FDG PET search strategy. *Nucl Med Commun* 2004 Dec;25(12):1187-1189.

21. Raijmakers PG, Paul MA, Lips P. Sentinel node detection in patients with thyroid carcinoma: a meta-analysis. *World J Surg* 2008 Sep;32(9):1961-1967.

22. Temmerman OP, Raijmakers PG, Berkhof J, Hoekstra OS, Teule GJ, Heyligers IC. Accuracy of diagnostic imaging techniques in the diagnosis of aseptic loosening of the femoral component of a hip prosthesis: a meta-analysis. *J Bone Joint Surg Br* 2005 Jun;87(6):781-785.

23. Juelsgaard P, Ronnow Sand NP. Somatic and social prognosis of patients with angina pectoris and normal coronary arteriography: a follow-up study. *Int J Cardiol* 1993 Apr;39(1):49-57.

24. Kronhaus KD, Lawson WE. Enhanced external counterpulsation is an effective treatment for Syndrome X. *Int J Cardiol* 2009 Jun 26;135(2):256-257.

25. de VJ, Dejongste MJ, Durenkamp A, Zijlstra F, Staal MJ. The sustained benefits of long-term neurostimulation in patients with refractory chest pain and normal coronary arteries. *Eur J Pain* 2007 Apr;11(3):360-365.

26. Sgueglia GA, Sestito A, Spinelli A, Cioni B, Infusino F, Papacci F, et al. Long-term follow-up of patients with cardiac syndrome X treated by spinal cord stimulation. *Heart* 2007 May;93(5):591-597.

27. Lanza GA, Sestito A, Sandric S, Cioni B, Tamburrini G, Barollo A, et al. Spinal cord stimulation in patients with refractory anginal pain and normal coronary arteries. *Ital Heart J* 2001 Jan;2(1):25-30.

28. Haude M, Baumgart D, Verna E, Piek JJ, Vrints C, Probst P, et al. Intracoronary Doppler- and quantitative coronary angiography-derived predictors of major adverse cardiac events after stent implantation. *Circulation* 2001 Mar 6;103(9):1212-1217.

29. Holmes DR, Jr., Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2010 Jul 20;56(4):321-341.

30. Lindsay J, Jr., Pinnow EE, Pichard AD. Frequency of major adverse cardiac events within one month of coronary angioplasty: a useful measure of operator performance. *J Am Coll Cardiol* 1999 Dec;34(7):1916-1923.

31. Rosano GM, Collins P, Kaski JC, Lindsay DC, Sarrel PM, Poole-Wilson PA. Syndrome X in women is associated with oestrogen deficiency. *Eur Heart J* 1995 May;16(5):610-614.

32. Rosano GM, Peters NS, Lefroy D, Lindsay DC, Sarrel PM, Collins P, et al. 17-beta-Estradiol therapy lessens angina in postmenopausal women with syndrome X. *J Am Coll Cardiol* 1996 Nov 15;28(6):1500-1505.

33. Shaw LJ, Min JK, Narula J, Lin F, Bairey-Merz CN, Callister TQ, et al. Sex differences in mortality associated with computed tomographic angiographic measurements of obstructive and nonobstructive coronary artery disease: an exploratory analysis. *Circ Cardiovasc Imaging* 2010 Jul 1;3(4):473-481.

34. Lanza GA, Sestito A, Iacovella S, Morlacchi L, Romagnoli E, Schiavoni G, et al. Relation between platelet response to exercise and coronary angiographic findings in patients with effort angina. *Circulation* 2003 Mar 18;107(10):1378-1382.

35. Sestito A, Maccallini A, Sgueglia GA, Infusino F, Larosa C, Aurigemma C, et al. Platelet reactivity in response to mental stress in syndrome X and in stable or unstable coronary artery disease. *Thromb Res* 2005;116(1):25-31.

36. Britten MB, Zeiher AM, Schachinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. *Coron Artery Dis* 2004 Aug;15(5):259-264.

37. Johnson BD, Shaw LJ, Buchthal SD, Bairey Merz CN, Kim HW, Scott KN, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004 Jun 22;109(24):2993-2999.

38. Sicari R, Palinkas A, Pasanisi EG, Venneri L, Picano E. Long-term survival of patients with chest pain syndrome and angiographically normal or near-normal coronary arteries: the additional prognostic value of dipyridamole echocardiography test (DET). *Eur Heart J* 2005 Oct;26(20):2136-2141.

39. Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. *Circulation* 2010 Jun 1;121(21):2317-2325.

40. Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM, et al. Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. *J Am Coll Cardiol* 2009 Jul 7;54(2):150-156.

41. 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 Aug 1;62(4):209-213.

42. Lanza GA, Buffon A, Sestito A, Natale L, Sgueglia GA, Galiuto L, et al. Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. *J Am Coll Cardiol* 2008 Jan 29;51(4):466-472.

43. Cannon RO, III, Quyyumi AA, Mincemoyer R, Stine AM, Gracely RH, Smith WB, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994 May 19;330(20):1411-1417.

44. Vermeltfoort IA, Raijmakers PG, Kamphuisen PW. Improved myocardial perfusion preceding clinical response on bosentan treatment for coronary vasospasm. *Acta Cardiol* 2009 Jun;64(3):415-417.

# Chapter 9

# Summary

# SUMMARY

A significant number of patients with angina pectoris and a positive stress test for ischaemia are found to have normal coronary arteries. This combination of symptoms and (apparent) circulatory normality is called cardiac syndrome X (CSX). Patients with CSX can experience much physical and mental distress and significant restrictions to leading a normal life.

**Chapter 1** is the introduction of the thesis and gives the summary of the proposed pathophysiologic explanation for CSX. Two mechanisms that are not mutually exclusive have been proposed: myocardial ischemia that might be caused by coronary microvascular dysfunction and enhanced sensitivity to intracardiac pain or the so-called "sensitive heart" syndrome. Secondly, the problem about incidence of CSX including the various test characteristics of non-invasive stress test was described. Finally, gender differences of angina and CSX are discussed.

**Chapter 2** reviews the literature (2003-2008) on the definition and incidence of CSX, using a standardized search strategy. We included 57 articles. Nine different inclusion criteria and forty-three exclusion criteria were found in the 57 articles. When these inclusion and exclusion criteria were applied to a sample population with normal coronary angiograms, treated during one year at a general hospital, the attributable CSX incidence varied between 3% (AP, positive stress test and normal CAG) and 11% (so-called 'broad diagnosis' CSX). This variation is considerable and shows that there is a need for a generally accepted definition of CSX. Contrasting study results may be due to these different applied inclusion characteristics. An additional aspect of the review, discussed also in Chapter 8, was to assess the often-proposed gender differences of CSX occurrence.

**Chapter 3** is a case history of patient with coronary spasms. Many of these patients suffer from persistent chest pain despite optimal medical treatment, and it has been suggested that patients with coronary spasm have a disturbance in the endothelial function of their coronary arteries. We used $^{15}O$-labeled $H_2O$ PET to assess myocardial perfusion and response to endothelin-receptor antagonist treatment. We measured an impaired coronary flow reserve (CFR) in 6 of 13 segments directly before the start of bosentan therapy. A repeated PET measurement after 16 weeks of bosentan treatment revealed a completely normalized CFR. Furthermore, the patient reported less frequent and less severe chest pain. Our data suggest a potential role of endothelin-receptor antagonists for patients with severe and persistent coronary vasospasms.

**Chapter 4** investigates the possible link between anxiety and ischaemia in CSX patients, whereby we obtained independent measurements of anxiety levels and the extent of ischaemia. The patients were screened with both the Trait and State Scales of the State-Trait Anxiety Inventory (STAI), and they all underwent myocardial perfusion scintigraphic imaging. Patients with a low trait anxiety had significantly less ischemic segments on the myocardial perfusion imaging than patients with a high trait anxiety (1.8 ± 1.9 vs. 3.5 ± 0.6, $p<0.05$). For state anxiety no significant differences could be found. These results showed that CSX patients with high trait anxiety are at risk of having more extended ischemia compared to CSX patients with low trait anxiety. This suggests that anxiety-induced ischemia can occur in CSX patients, and that high trait anxiety might be a predisposing risk factor for microvascular dysfunction and/or ischaemia causing reversible perfusion defects on the SPECT imaging of CSX patients.

**Chapter 5** describes the use of first-pass perfusion cardiac magnetic resonance (CMR) to semi-quantitatively assess subendocardial and subepicardial myocardial blood flow in 20 CSX patients. As hypothesized, and already described by a single CMR study, subendocardial hypoperfusion might be present in CSX patients. In our CMR investigation a myocardial perfusion index (MPI) was calculated using the normalized upslope of myocardial signal enhancement. An index for myocardial perfusion reserve (MPRI) was calculated by dividing the MPI values at maximal vasodilatation by the values at rest. The MPI in our study population increased significantly during adenosine infusion in both the subendocardium (from 0.091 ± 0.020 to 0.143 ± 0.030: $p<0.001$) and the subepicardium (from 0.074 ± 0.017 to 0.135 ± 0.03: $p<0.001$). Both the resting and stressed states the subendocardial MPI was higher than the subepicardial MPI: respectively 0.091 ± 0.020 versus 0.074 ± 0.017 ($p<0.001$), and 0.143 ± 0.030 versus 0.135 ± 0.03 ($p=0.021$). There was a significant difference between the myocardial perfusion reserve index (MPRI) in the subendocardium, 1.67 ± 0.38 and the subepicardium, 1.98 ± 0.64 ($p=0.001$). The mean subendocardial**:** subepicardial MPRI ratio was 0.91 ± 0.11. None of the patients had a subendocardial**:** subepicardial MPRI ratio less than 0.72, which has been proposed as the optimal cut-off for distinguishing between normal controls and subendocardial hypoperfusion in patients with syndrome X.
We found no evidence for subendocardial hypoperfusion in patients with syndrome X. However, on our first-pass CMR images we found initial dark rim artefacts in the subendocardium in all patients. This temporary signal loss is considered to be an artefact related to the first pass sequence and is not typical for an ischaemia related defect which shows a more sustained signal loss. Our results support the idea that these artefacts have been mistaken for subendocardial hypoperfusion by Panting et al.

**Chapter 6** investigates the correlation between stress CMR and single photon emission computed tomography (SPECT) imaging, using regional flow analysis instead of global

MBF evaluation for 20 CSX patients. This investigation was to check the hypothesis that focal ischaemia occurs in relatively small myocardial regions scattered throughout the myocardium. Both the CMR and SPECT data showed in about 10% of all segments stress-induced myocardial perfusion abnormalities, which would appear to suggest focal ischaemia and patchy distributions. Of course, on the other hand, these differences might be related to possible false results of non-invasive techniques. Interestingly, the stress induced perfusion abnormalities were found in different regions of the CMR and SPECT images of the same patients. Due to the time delay between the CMR and SPECT stress tests the regional mismatch of the CMR and SPECT results, may be the result of transient focal ischaemia. We did not demonstrate a regional match of ischaemia between CMR and SPECT studies, this makes microvascular dysfunction in certain fixed coronary territories unlikely. If microvascular dysfunction is associated with ischaemia in CSX patients it may not be an irreversible pathophysiological phenomenon but rather a temporary malfunction or dysregulation. Hence, subclinical atherosclerosis may be compatible with transient focal ischaemia in CSX patients.
But if microvascular dysfunction is the case in CSX, the abnormality may not involve all coronary microvessels of a major coronary branch uniformly, but may be distributed in a patchy scattered manner. CAG only detects epicardial lesions and is unable to obtain objective evidence for this kind of myocardial ischaemia. Hence, our results could be due to the time-dependent variability of the mechanisms responsible for microvascular dysfunction, i.e. due to so-called transient ischaemia.

**Chapter 7** gives the results of cardiac PET measurements of subendocardial and subepicardial myocardial blood flow in normal healthy controls. Since PET measurements of transmural myocardial blood flow with $^{15}$O-labeled water are currently the gold standard, the technique can be used as a tool to assess subendocardial ischaemia in patient populations. However, only very limited data are available regarding subendocardial and subepicardial MBF measurements with $^{15}$O-labeled water PET, and data in normal controls are lacking. In the present study a population of 27 subjects was included without angina pectoris and a mean age of 41 years. Mean rest MBF was 1.46 ± 0.49 in the subendocardium, and 1.14 ± 0.342 $ml \cdot min^{-1} \cdot g^{-1}$ in the subepicardium ($p<0.001$). Stress MBF during adenosine increased to a greater extent at the subepicardial level (subendocardium vs. subepicardium: 3.88 ± 0.86 vs. 4.14 ± 0.88 $ml \cdot min^{-1} \cdot g^{-1}$, $p=0.013$). The endocardial-to-epicardial MBF ratio decreased significantly during hyperaemia (1.35 ± 0.23 to 1.12 ± 0.20, $p<0.001$). Hyperaemic transmural MBF was inversely correlated with left ventricular end-diastolic volume index (LVEDVI) ($r^2=0.41$, $p=0.0003$), with greater impact at the subendocardial level.
$^{15}$O-labeled water PET enables MBF measurements with distinction of the subendocardial and subepicardial layers in the normal human heart and correlates with LVEDVI. This

PET technique may prove useful in evaluating patients with signs of ischaemia due to coronary artery disease or microvascular dysfunction.



Finally, **chapter 8** reviews the prognosis of CSX, which is generally reported as good, although a recent study reported an adverse outcome for women. Furthermore, it is stated that (pre-menopausal) women are prone to develop CSX, and some studies are focused only upon female patients. The objective of this review and meta-analysis was to evaluate the risk of a major cardiac event and the risk of persistent symptoms in different CSX patient populations. Additionally, we determined the existence and extent of the predominance of women in CSX patient populations. Sixteen studies, comprising a total of 1694 patients, met the inclusion criteria and were included in the review. With respect to CSX prognosis, it turns out that the overall major cardiac event rate for CSX patients is 1.5% per 5 years. This represents a *better* prognosis compared to the general population, suggesting that CSX patients may benefit from protective factors against coronary macrovascular disease. However, because angina pectoris in CSX is recurrent and persistent in 55% of the patients, it represents a significant impairment of the quality of life. With respect to gender, our review demonstrated that the pooled proportion of female CSX patients is 49%. This argues against the generally accepted opinion and statements that CSX occurs typically or preferentially in women.

# Conclusions and Future Perspectives

# CONCLUSIONS AND FUTURE PERSPECTIVES



'Chest pain with normal coronary angiograms: is the heart innocent or guilty?' is the title of a review paper (1) in 1990 by Cannon (Bethesda, Maryland). Cannon's recent paper 'microvascular angina and the continuing dilemma of chest pain with normal coronary angiograms' summarizes the current knowledge on the pathophysiology, diagnosis and management of cardiac syndrome X (CSX) (2). Most important, in his opinion, remains the need for advanced imaging technology to resolve the mechanism that links coronary microvascular dysfunction to myocardial ischaemia

## Mental stress and endothelial dysfunction

In the present thesis we found a relation between anxiety and the extent of ischaemia in CSX patients.
The atherogenic effect of anxiety is becoming increasingly clear, as a recent long-term study by Janszky (3) showed. This study involved nearly 50,000 young Swedish men between the ages of 18 and 20 years, with a follow-up of 37 years. It was found that anxiety, as diagnosed according to ICD-8 criteria, provided independent predictions of coronary heart disease.

With regard to the pathophysiology of CSX this phenomenon of 'mental stress ischaemia' may be an important contributor to microvascular dysfunction. Mental stress, especially anxiety, causes endothelial dysfunction (via endothelin-A receptors) and results in atherosclerosis (4).

Looking to the future, there are two possible studies that readily come to mind:

(1) A randomized, controlled trial investigating the possible influence of anxiety-regulating mind-body therapy (autogenic training, tai chi) on CSX. Such a trial could provide more insight into the pathophysiology of stress-induced ischaemia in CSX patients, especially if it were combined and compared with the scanning of patients deliberately subjected to mental stress.
(2) A randomized intervention trial using an endothelin-receptor antagonist. Endothelial dysfunction is frequently described in CSX patients, and our limited data suggest a potential role of endothelin-receptor antagonists for patients with severe coronary vasospasms. An endothelin-receptor antagonist study is best done using cardiac PET to measure the MBF.

These studies could be extended with an adenosine stress study that includes measurements of the sCD40 ligand. This possibility was recently suggested by

Kaski (St. George University of London, and a world authority on CSX) because the sCD40 molecule is inflammatory and could play a role in the pathogenesis of CSX. Furthermore, Kaski suggested that oestrogen depletion might also play a pathologic role in endothelial dysfunction in CSX. This suggestion arises from Kaski's focus on peri- or postmenopausal women.

In more detail, Kaski considers that abnormal pain perception may contribute to the genesis of CSX, and that oestrogen plays an important part in the pain perception. Oestrogen receptors are expressed in cells of the cardiovascular system and modulate vasomotor tone as a result of a rapid vasodilator effect. Furthermore, changes in women's oestrogen concentrations modulate the natural ability of the brain to suppress pain. When oestrogen values are high, the brain's natural anti-nociceptive system responds in a stronger fashion to painful stimuli, releasing endorphins than dampen the pain signals received by the brain. When oestrogen is low, the system does not control pain as efficiently. The consequence is that low oestrogen levels are associated with endothelial dysfunction and an impaired function of the natural endogenous opioid system, resulting in increased pain perception.

Kaski recommends studying short-term oestrogen therapy in larger cohorts, before individual patients start long-term oestrogen medication. From the above considerations it is possible that oestrogen therapy might reduce anginal episodes and improve myocardial blood flow. More generally, Kaski advises a multidisciplinary approach that involves cardiologists, general physicians, pain units and psychologists, together with prone 'hot' lines or internet 'clinics' to reduce unnecessary hospital re-admissions.

## Future imaging technology for diagnosing CSX

Today CAG is a necessary step in the diagnosis of patients suspected to have CSX. This diagnostic method outlines the lumina of the coronary arteries and can be used to exclude significant coronary obstruction. However, CAG provides no information about the arterial wall, and severe atherosclerosis that does not encroach on the lumen may go undetected. Therefore myocardial perfusion imaging (e.g. PET) will be mandatory in the future.

Other disadvantages of CAG are the complications. This invasive test carries a 1 in 1000 risk of stroke or myocardial infarction; and there are other problems such as transient tachy- or bradyarrhythmias, or bruising or bleeding at the catheter insertion site, although these problems occur in less than 1% of patients. Finally, the contrast agents can provoke side effects like hypotension, nausea, a warm sensation, and transient deterioration of renal function.

In this light, non-invasive structural imaging like Coronary CT angiography (CTA) might be of interest. In the diagnostic work-up of coronary artery disease the emerging capabilities of CT imaging compete with many other well-established and readily available diagnostic modalities. However, CT imaging is prone to artefacts, because

it stretches the temporal and spatial resolution of CT scanners. The artefacts include those due to motion, which typically blurs the contours of the coronary arteries. Also, the partial volume in CT leads to overestimating the dimensions of high-intensity objects (e.g. calcification within coronary arteries) and may cause difficulties in image interpretation (5). The technology of cardiac CT will continue to progress. Whereas radiation exposure sets a limit to increases in spatial resolution, temporal resolution will likely be increased considerably, thereby reducing the artifacts. Careful clinical studies of appropriate size and design will be needed to clarify the role of coronary CTA in CSX. Although CTA cannot presently be considered a routine replacement for invasive coronary angiography, it is conceivable that CTA in combination with positron emission tomography (PET) will be clinically applied to rule out coronary stenoses in patients suspected of having CSX. Hybrid imaging of CTA with PET is rapidly emerging. Cardiac CTA/PET allows quantification of cardiac perfusion in combination with assessment of coronary anatomy within a single scanning session of less than 45 minutes. The important technical advantages of PET compared to SPECT (e.g. the attenuation correction, the high spatial resolution, and high extraction fraction of the ideal PET tracers) result in a sensitivity and specificity of 92-93%. The low radiation burden is another important advantage. The near-simultaneous anatomical evaluation of coronary arteries using CT and their corresponding functional status using PET provide a wealth of complementary information about patients being evaluated for suspected CSX (5).

Patients with AP, abnormal stress test and normal CAG are a common occurrence for all cardiologists. Using the CSX incidence data of a general hospital in 2003 it can be assumed there are about 5000 new CSX patients in the Netherlands per year. Hence, a cardiologist has a limited experience with CSX patients.

A standard diagnostic work-up of CSX patients in CSX expertise centres could be useful for further studies. More specifically, CSX expertise centres with larger populations of CSX patients than seen in general hospitals may make intervention studies possible, for example a psychological treatment or an interventional medical therapy combined with advanced imaging technology (e.g. cardiac gated PET-CT, gated PET-MRI).

Since advanced imaging technology may be necessary, such 'CSX centres of excellence' would have state-of-the-art equipment, like cardiac gated PET-CT or gated PET-MRI. For example, microvascular dysfunction is best detected in the subendocardium, since ischaemia nearly always begins there. Subendocardial ischaemia has been described in CSX patients (6), although in our study we found no evidence of it. Hence further studies with cardiac PET (with $^{15}$O-labelled water or $^{82}$Rb) or MRI may be necessary to detect possible subendocardial ischaemia in CSX patients. Also, quantitative measurements of both the subendocardial and the subepicardial myocardial blood flow would enable an objective evaluation of potential new therapies.

Finally, we suggest (a) further research into subendocardial perfusion in CSX patients using $^{15}$O-labelled water 4D-gated PET/CT; (b) multicentre studies in combination with current best practice; and (c) the development of professional guidelines for diagnosis and treatment of CSX.

# REFERENCE LIST


1. Cannon RO, III. Chest pain with normal coronary angiograms: is the heart innocent or guilty? *J Am Coll Cardiol* 1990 Sep;16(3):596-598.
2. Cannon RO, III. Microvascular angina and the continuing dilemma of chest pain with normal coronary angiograms. *J Am Coll Cardiol* 2009 Sep 1;54(10):877-885.
3. Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. *J Am Coll Cardiol* 2010 Jun 29;56(1):31-37.
4. Spieker LE, Hurlimann D, Ruschitzka F, Corti R, Enseleit F, Shaw S, et al. Mental stress induces prolonged endothelial dysfunction via endothelin-A receptors. *Circulation* 2002 Jun 18;105(24):2817-2820.
5. Knaapen P et al. Cardiac PET-CT: advanced hybrid imaging for the detection of coronary artery disease. *Neth Heart J*.
6. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002 Jun 20;346(25):1948-1953.

# Nederlandse samenvatting

# NEDERLANDSE SAMENVATTING



Ongeveer 20% van alle patiënten die een hartkatheterisatie (CAG) ondergaan wegens pijn op de borst, hebben normale kransslagaderen. Wanneer er bij deze patiënten ook tekenen zijn van zuurstoftekort van de hartspier, zoals een positieve inspanningstest of een positieve hartscan, wordt gesproken van cardiaal syndroom X (CSX).
Hoewel de prognose van deze patiënten goed is, beperken de heftige recidiverende thoracale pijnklachten het dagelijkse leven van deze patiënten. Dit leidt tot herhaalde ziekenhuisopnamen, arbeidsongeschiktheid en een grote psychische belasting.

## Hoofdstuk 1

Hoofdstuk 1 is de introductie van dit proefschrift en geeft een samenvatting van de mogelijke oorzaken van cardiaal syndroom X. Enerzijds zou een grotere gevoeligheid voor pijn, het zogenaamde "hypersensitieve hart", een rol kunnen spelen. Anderzijds worden aanwijzingen gevonden voor zuurstof tekort van de hartspier (myocard), veroorzaakt door het niet goed functioneren van de kleinste bloedvaten (haarvaten), coronaire microvasculaire dysfunctie genoemd.
In de introductie wordt eveneens de controverse rondom de diagnose CSX beschreven. In de literatuur zijn er verscheidene criteria voor het stellen van de diagnose CSX. Dit leidt tot heterogene studiegroepen. Daarnaast is het belangrijk te realiseren dat geen enkele niet-invasieve stresstest perfect is.
Tenslotte wordt er ingegaan op interraciale en sekseverschillen.

## Hoofdstuk 2

Er zijn geen exacte cijfers bekend over hoe vaak syndroom X voorkomt. Daartoe hebben we retrospectief onderzocht hoeveel patiënten we gedurende 1 jaar tegenkwamen in een groot perifeer ziekenhuis in Nederland. Voorts bespreken we middels een gestandaardiseerde zoekstrategie de verschillende gehanteerde CSX definities in de literatuur (periode 2003-2008). We identificeerden uiteindelijk 57 artikelen (totaal aantal patiënten: n=2375), die de basis vormden voor dit review. Deze 57 studies toonden veel variatie in de gehanteerde criteria voor de diagnose CSX: 9 verschillende inclusiecriteria en 43 verschillende exclusie criteria. Afhankelijk van de gehanteerde definitie vonden we een incidentie variërend van 3% tot 11% van alle CAG patiënten. Gezien het grote effect van de verschillende definities op de incidentie van CSX, blijkt dat er een noodzaak is aan een uniforme definitiestelling voor cardiaal syndroom X. Daarnaast vonden wij in het review dat slechts een kleine meerderheid van de CSX patiënten vrouw is. CSX lijkt dus geen typische vrouwenziekte te zijn, wat vaak wordt beweerd in studieboeken en overviews.

## Hoofdstuk 3

Hoofdstuk 3 beschrijft een ziekte geschiedenis van een patiënt met coronaire spasmen. Veel van deze patiënten hebben last van hardnekkige pijn op de borst, ondanks optimale medische behandeling. Enkele studies hebben gesuggereerd dat patiënten met coronaire spasmen een verstoring in de endotheliale functie van de kransslagaderen hebben. We hebben deze patiënt 16 weken met de endotheline-receptor antagonist bosentan behandeld. Positron emissie tomografie (PET) met gebruik van radioactieve tracers zoals zuurstof-15-gelabeld water maakt het mogelijk myocardperfusie te meten in absolute zin. Het effect van de bosentan behandeling hebben wij middels PET gemeten. Direct vóór de aanvang van behandeling met bosentan maten wij een verminderde doorbloeding na farmacologische stress in 6 van 13 segmenten in het hart. De herhaalde PET meting na 16 weken bosentan behandeling toonde een volledig genormaliseerd perfusie na stress. Bovendien vertelde patiënt minder frequent en minder ernstig pijn op de borst klachten te ondervinden tijdens de bosentan therapie. Deze resultaten zouden kunnen wijzen op een rol van endotheline-receptor antagonisten bij patiënten met coronaire vasospasmen.

## Hoofdstuk 4

Het zuurstoftekort van de hartspier in CSX patiënten zou o.a. veroorzaakt kunnen worden door mentale stress zoals angst. We hebben in dit hoofdstuk het mogelijke verband tussen angst en ischemie in CSX patiënten onderzocht. De patiënten werden gescreend op angst middels de gevalideerde State-Trait Anxiety Inventory (STAI). Daarnaast ondergingen alle patiënten een myocardperfusiescan. Patiënten met een lage angstdispositie hadden aanzienlijk minder zuurstoftekort op de hartscan, dan patiënten met een hoge angstdispositie (1,8 ± 1,9 versus 3,5 ± 0,6, $p < 0,05$). De aanleg om angstig te zijn is een risicofactor voor de uitgebreidheid van het zuurstoftekort van de hartspier bij CSX patiënten.
Deze bevindingen suggereren dat angst-geïnduceerde ischemie kan optreden bij CSX patiënten.

## Hoofdstuk 5

Hoofdstuk 5 beschrijft een cardiale MRI (CMR) studie welke de hartspier van patiënten met CSX in meer detail bestudeert. Algemeen wordt gedacht dat de binnenste helft van de hartspier ('subendocardiale deel') eerder een zuurstoftekort heeft in vergelijking met de buitenste helft ('subepicardiale deel') van het hart. Cardiale MRI maakt het mogelijk deze twee delen te bestuderen. De hypothese was dat CSX veroorzaakt zou worden door verminderde perfusie in de binnenzijde van de hartspier na stress, zoals beschreven in één eerdere CMR studie.

Middels CMR werd de myocard perfusie index (MPI) zowel in rust als in stress (adenosine) gemeten, alsmede de index voor myocard perfusie reserve (MPRI), in zowel de subendocardiale als subepicardiale laag van het hart.
Er was een goede en gelijkwaardige perfusie toename in stress in onze studie populatie in zowel het subendocard als in het subepicardium.
We vonden geen bewijs voor subendocardiale hypoperfusie bij patiënten met het syndroom X.

## Hoofdstuk 6

In hoofdstuk 6 wordt de correlatie tussen CMR en myocardscan Single Photon Emission Computed Tomografie (SPECT) onderzocht in CSX patiënten.
In dit onderzoek wordt specifieker naar de regionale doorbloeding gekeken. Bij de eerdere studie werd gekeken naar de globale doorbloeding van de subendocardiale en subepicardiale laag. Hierbij wordt geen rekening gehouden met potentiële regionale verschillen in doorbloeding. Gezien het feit dat drie verschillende kransslagaderen de doorbloeding van de linker harthelft verzorgen is een regionale analyse van belang. De linker zijde van het hart wordt hierbij onderverdeeld in 19 segmenten, volgens de richtlijnen van American Heart Association.
De hypothese was dat de ischemie in CSX heel focaal in kleine gebieden verspreid in het hart optreedt. Zowel de CMR als de SPECT scans toonden in ongeveer 10% van alle segmenten ischemie. Echter de locatie van de ischemie kwam in beide onderzoeken niet met elkaar overeen. Deze mismatch zou kunnen worden veroorzaakt door voorbijgaande focale ischemie. De microvasculaire dysfunctie is dan blijkbaar niet gerelateerd aan een vaste kransslagader, maar kan wisselen. Natuurlijk kunnen onze bevindingen ook vals-positief voor ischemie zijn, inherent aan elke niet-invasieve beeldvormende test. Echter de ‘gouden standaard’ hartkatheterisatie (CAG) brengt alleen de epicardiale kransslagaderen in beeld. Onderzoeken waarbij de doorbloeding van de hartspier wordt bestudeerd (bijv. met SPECT of MRI) kunnen beïnvloed worden door afwijkingen in de kransslagaderen (zichtbaar te maken met de CAG) maar ook door afwijkingen in de kleine vaten (zogenaamde microvasculaire dysfunctie). De CAG kan microvasculaire dysfunctie niet detecteren, zodat de CAG slechts ten dele geldt als een gouden standaard voor onderzoeken die de hartspier doorbloeding meten.

## Hoofdstuk 7

Positron emissie tomografie (PET) met gebruik van zuurstof-15-gelabeld water is momenteel de gouden standaard voor het meten van transmurale myocard perfusie in absolute zin. Ischemie begint meestal aan de binnenzijde van het hart (subendocard). Het is dus belangrijk om een techniek te ontwikkelen welke de absolute perfusie in het subendocard kan meten. Er zijn in de literatuur enkele studies bekend welke subendocardiaal en subepicardiale perfusie metingen middels PET hebben verricht,

echter perfusiemetingen in normale controle personen ontbreken. Hoofdstuk 7 beschrijft de zuurstof-15-gelabeld water PET studie, welke de subendocardiale en de subepicardiale perfusie meet in 27 gezonde proefpersonen. In rust was de perfusie 1,46 ± 0,49 in de subendocard, en 1,14 ± 0,342 ml · $min^{-1}$ · $g^{-1}$ in het subepicardium ($p < 0,001$). Tijdens stress neemt de perfusie in het subepicard meer toe vergeleken met het subendocard. Zuurstof-15-gelabeld water PET maakt perfusie metingen met onderscheid tussen de subendocardium en subepicardium mogelijk in het normale menselijke hart. Deze PET-techniek kan in de toekomst nuttig zijn in de diagnostiek van patiënten verdacht voor zowel primaire (CSX) als secundaire microvasculaire dysfunctie.

## Hoofdstuk 8

Hoofdstuk 8 bespreekt de prognose van patiënten met CSX. In studieboeken en in overviews wordt gesteld dat de prognose van CSX goed is. Echter recentelijk rapporteerde een studie een negatieve uitkomst voor vrouwen met angina pectoris en normale kransslagaders. In dit review wordt de prognose beschreven. Zestien studies (totaal 1694 patiënten) voldeden aan de inclusie criteria. De kans op een major cardiac event zoals een myocard infarct, dood door hart-en vaatziekte of noodzaak tot revascularisatie voor CSX patiënten is 1,5% per 5 jaar. Dit zou kunnen betekenen dat CSX patiënten zelfs een betere prognose hebben in vergelijking met de algemene bevolking. De angina pectoris blijft echter in 55% van alle patiënten bestaan. Hoewel de prognose van deze patiënten dus goed is, beperken de heftige recidiverende thoracale pijnklachten het dagelijks leven van deze patiënten.

# TOEKOMST PERSPECTIEVEN

Voor de evaluatie van de kransslagaders is de hartkatheterisatie essentieel. Aangezien patiënten met CSX normale kransslagaders hebben, is de hartkatheterisatie ook noodzakelijk om de diagnose CSX te stellen. Er wordt veel onderzoek verricht naar niet-invasieve technieken die belangrijke epicardiale stenosen kunnen uitsluiten en idealiter tegelijkertijd microvasculaire dysfunctie kunnen opsporen.



Niet-invasieve cardiale beeldvorming, zoals coronaire CT-angiografie (CTA) is sterk in ontwikkeling. Hoewel CTA (momenteel) niet kan worden beschouwd als een routinematige vervanging voor de invasieve coronaire angiografie, is het denkbaar dat CTA in combinatie met positron emissie tomografie (PET) in de toekomst bij patiënten verdacht voor CSX kan worden toegepast. De bijna gelijktijdige anatomische evaluatie van de kransslagaderen middels CTA en de bijbehorende kwantificatie van de perfusie verkregen met de PET geeft veel informatie in een totale onderzoeksduur van slechts 45 minuten.
In de toekomst is nog veel ontwikkeling te verwachten van nieuwe PET tracers, zoals radioliganden voor de endotheline-receptor, de angiotensine II type 1 receptor en het adrenerge systeem, evenals vooruitgang in de cardiale PET software and hardware technologie, zoals de gated PET en de combinatie van PET met MRI.
De introductie van gated PET/CTA of PET/MRI maakt onderzoek naar subendocardiale perfusie, oa. bij patiënten met verdenking op CSX, met behulp van zuurstof-15-gelabeld water potentieel betrouwbaarder.
Verder zou het wenselijk zijn om in de toekomst de zorg rondom CSX te verbeteren. Evenals in vooraanstaande centra (University of Bologna, Instituta Cardiologica Roma, St. George's Hospital London, Chicago, Hammersmith Hospital London, Brigham and Women's Hospital Boston, Cedar-Sinai Medical Center, Los Angeles) moet gekozen worden voor een multidisciplinaire benadering, waar oa. de psychologie niet kan worden gemist.
Waar het gaat om het wetenschappelijk onderzoek en de ontwikkeling van evidence based richtlijnen moet gestreefd worden naar (inter)nationale samenwerking.

# Dankwoord

# DANKWOORD



Mijn oprechte dank gaat uit naar allen die, op enigerlei directe of indirecte wijze, hebben bijgedragen aan de totstandkoming van dit proefschrift. Een aantal daarvan wil ik graag met name noemen:

Allereerst de patiënten die vrijwillig mee hebben gedaan aan dit onderzoek.

Prof. dr. G.J.J. Teule, beste Jaap. De wijze waarop je mij afgelopen jaren deelgenoot maakte van je originele visionaire ideeën, heeft me geleerd buiten de gebaande paden te denken. Ik heb respect voor je gedrevenheid, inzicht en kennis. Je hebt me dikwijls terzijde gestaan met wijze raad op professioneel gebied, maar ook zeker in mijn persoonlijk leven. Jaap, ik ben je enorm dankbaar voor alle geestige, inspirerende, strategische, innovatieve, intelligente verhandelingen die je met me deelt, maar vooral dat je altijd met me mee wil denken.

Dr. P.G.H.M. Raijmakers, beste Pieter. Dank voor je begeleiding, kritische commentaar en op de goede momenten bemoedigende woorden. We hebben samen bijzonder veel plezier gehad. Ik hoop dat ik nog veel met je mag samenwerken.

Prof. dr. O.S. Hoekstra, beste Otto. Je bood me altijd een luisterend oor, liet je gedachten over het probleem gaan, en kwam meestal met inspirerende adviezen (botaniseren!). Met veel plezier heb ik met je gewerkt. Dank voor het vertrouwen dat je in me stelde.

Prof. dr. A.C. van Rossum, beste Bert, u reageerde meteen enthousiast op mijn voorstel tot CSX-CMR onderzoek in 2004. Dit heeft geresulteerd in een belangrijke bijdrage aan het proefschrift. Hartelijk dank voor de CMR stage en de belangstelling die u bent blijven tonen.

Prof. dr. G.J. Tangelder, Dr. R.H.J.A. Slart, Dr. H.J. Muntinga, hartelijk dank voor de genomen tijd ter beoordeling van het proefschrift.

Dr. M. van der Vis-Melsen, Dr. A. Zwijnenburg, beste Mary en Ton, op een middag in 2004 bedachten we dit plan samen met Jaap in de kelder, terwijl we voor de derde keer naar de afwijkende SPECT van een patiënt keken met normale CAG. Ontstaan als idee voor 1 artikel werd gaandeweg een hele thesis. Dank voor alles wat ik van jullie mocht leren in het Spaarne Ziekenhuis.

Medewerkers nucleaire geneeskunde Spaarne Ziekenhuis. Jullie waren onmisbaar voor dit onderzoek: het tevoorschijn toveren van oude scans, extra patiënten scannen, printers repareren en natuurlijk jullie hartelijkheid op de afdeling.

Cardiologen Spaarne Ziekenhuis 2004, Dr. van Doorn, Dr. Ezechiëls, Dr. Wesdorp en natuurlijk Dr. Odekerken en Dr. Kuijper, dank voor het herbeoodelen van een honderdtal CAG's. Met jullie humor wisten we de vaart er wel in te houden. Ook dank aan mevrouw Bos.

Prof. dr. Emile Comans, Dr. Bart van Berckel, Dr. Jan Roos, Dr. Rik Pijpers, Annelies van Schie, Dr. Corneline Hoekstra, Reiny Kooistra, Mohammed Akkariou, Joris Tim, Nafees Rizvi, Daniela Oprea, Sandra Srbljin, nucleair geneeskundigen, het was een genoegen om met jullie te werken in de VU.
Prof. A. Lammertsma, Dr. Ronald Boellaard, Dr. Mark Lubberink, Dr. Arthur van Lingen, Amanda Kroonenberg-Kalwij, Jaap van der Kuij, Reina Kloet, Saskia Cornielje en alle MNW'ers en medewerkers NG-PET veel dank voor jullie ondersteuning.

Dr. P. Knaapen, beste Paul, jouw passie voor het vak tezamen met je uitgebreide kennis, maakten het heel uitdagend om met jou te discussiëren.

Dr. A.M. Beek, O. Bondarenko, M Belderok, beste Aernout, Olga en Mary, ondanks jullie drukke schema's maakten jullie tijd voor mijn CSX patiënten. Dank voor de bijdragen aan de CMR studies.

Beste Dr. Olivier Temmerman, Dr. Bas Holverda en Bart Wittgen, door de jaren heen hebben jullie mij semilegaal voorzien van veel software, vergezeld van nuttige tips en grapjes. Dank daarvoor.

Dr. Pieter Willem Kamphuisen, je belde ons vanuit het AMC met een klinisch probleem, gevolgd door prettige emails, uiteindelijk resulterend in ons case report. Misschien dat mijn promotie de gelegenheid is om nu eens kennis te maken?

Beste Ingrid Riphagen, wat een werk waren al die losgekoppelde referenties. Dank!

Alle medewerkers van het Verbeeten Instituut, in het bijzonder Arjan van Dijk, Gerard Tijmes en Thed Naber, dank voor jullie interesse, ondersteuning en de tijd die ik kreeg om mijn proefschrift af te ronden.

Mijn ooms, tantes, neven, nichten, vrienden, vriendinnen. Hartelijk dank voor alles wat helemaal niets met dit onderzoek te maken had!

Oom Russell, onbeschrijfbaar hoeveel van waarde je bent geweest.

Mijn paranimfen Ilona, dierbare vriendin en Koen, oudste broer, fijn dat jullie naast me staan tijdens dit spannende moment.

Mijn zus Pit, broers Nard en Koen, schoonouders, schoonzussen en zwagers, dank voor de gezelligheid, steun en interesse.

Pa en ma, eindelijk is het dan zover. Het proefschrift is klaar. De hulp bij het verzorgen van de kinderen, stimulerende gesprekken en genegenheid hebben geresulteerd in deze mijlpaal. Jullie instelling van altijd vrolijk doorzetten en nooit opgeven, hoop ik door te geven aan jullie kleinkinderen.

Lieve Hidde, Hannah en Julia, mijn allerliefsten.

Hugo, jij en ik & ik en jij.....ik heb je lief.

# Curriculum Vitae

# CURRICULUM VITAE



Ilse Anne Christien Vermeltfoort was born on February 11th 1974 in Eindhoven, the Netherlands. She grew up in Waalre, near Eindhoven, together with her two brothers and sister. Her secondary education was at the St Joris College in Eindhoven.

Ilse began studying Medicine in 1992 at Ghent University in Belgium. She moved back to the Netherlands to continue and complete her study at the Erasmus University in Rotterdam.

After graduating from Medical School in 1999, Ilse worked in the Department of Cardiology at the Reinier de Graaf Hospital in Delft. In 2000 she moved to the Maastricht University Medical Centre to start her Specialist's training in Cardiology under the supervision of Dr. E.C. Cheriex.

In 2002 Ilse began a Residency in Nuclear Medicine at the VU University Medical Centre, Amsterdam, supervised by Prof. Dr. G.J.J. Teule. She started the research that resulted in the present thesis during her training period with Dr. S.C.C. Reinders Folmer and Dr. A. Zwijnenburg in Spaarne Hospital, Haarlem.

After completing her Residency in 2006, Ilse worked as a Nuclear Physician in the VU University Medical Centre for three years with Prof. Dr. O.S. Hoekstra. Since October 2009 she has been a staff member at the Verbeeten Institute in Tilburg.

Ilse is married to Hugo Rutten. They have a son, Hidde, and two daughters, Hannah and Julia.

# Abbreviations

# ABBREVIATIONS

Abbreviations used in this thesis are:

| | |
|---|---|
| AP: | angina pectoris |
| CAD: | coronary artery disease |
| CAG: | coronary angiography |
| CBF: | coronary blood flow |
| CFR: | coronary flow reserve |
| CMR: | cardiac magnetic resonance |
| CMVD: | coronary microvascular dysfunction |
| CSX: | cardiac syndrome X |
| ECG: | electrocardiography |
| LV: | left ventricular |
| LVEDV: | left ventricular end-diastolic volume |
| LVEDVI: | left ventricular end-diastolic volume index |
| LVESV: | left ventricular end-systolic volume |
| LVEF: | left ventricular ejection fraction |
| MACE: | major adverse cardiac event |
| MBF: | myocardial blood flow |
| MPI: | myocardial perfusion index |
| MPRI: | myocardial perfusion reserve index |
| NCA: | normal coronary arteries |
| PET: | positron emission tomography |
| SPECT: | single photon emission computed tomography |
| STAI: | state-trait anxiety inventory |
| VSMC: | vascular smooth muscle cells |