Normal versus hypertrophic wound healing

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Chapter 5

Possible association of scar hypertrophy with recurrent angina after Coronary Artery Bypass Grafting

Abstract

Hypertrophic scaring occurs in a considerable number of surgical scars and seems to have common features with the processes of atherosclerosis in coronary artery disease and intima hyperplasia in graft failure. Coronary artery disease and graft failure are associated with recurrent angina.

In a prospective study the relationship between hypertrophic scarring and the occurrence of recurrent angina after coronary artery bypass grafting was investigated. Patients who underwent coronary artery bypass grafting with a median sternotomy were included in the study and divided into two groups according to the presence or absence of hypertrophic scarring. After a mean follow up of two years, patient information was collected. The primary endpoint was the occurrence of recurrent angina. Seventy patients (55 men, mean age 67.8 ± 9.8 years) were included.

Hypertrophic scarring occurred in 29 patients (41%). The groups were comparable with respect to their baseline characteristics. No significant difference of the occurrence of recurrent angina was observed ($p = 0.180$). In conclusion, this prospective study did not discover an association between hypertrophic scarring and recurrent angina after coronary artery bypass grafting.

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Introduction

Hypertrophic scars (HTS) are a complex problem and occur in 39-68% of surgical scars and in 33-91% of burn scars[1]. The prevalence of HTS varies from 15-30% in Caucasians, up to 94% in Asians[2]. HTS are defined as overgrowths of fibrotic tissue which remain within the boundaries of the original wound[3]. HTS typically are raised, red and itchy firm lesions and may cause pain or even restriction when surrounding a joint[4]. One of the predilection areas on the body is the presternal region[5].

Repair in the form of fibrosis occurs in many tissues and is generally preceded by an increased production of pro-inflammatory growth factors and cytokines as well as an increased influx of inflammatory cells[1,4,6,7]. Coronary atherosclerosis/coronary artery disease, coronary artery bypass graft (CABG) failure and HTS have these features in common.

In atherosclerosis there is an altered platelet activation state, there is infiltration of the vessel wall by leukocytes (including macrophages) and specific cytokines and growth factors are present including CCL2 and TNF-α[8]. Mid-term graft occlusion is the result of hyperplasia of the intima which forms a foundation for atherosclerosis. This abnormal vessel wall wound healing results from excessive growth factor and cytokine production by platelets, leukocytes and endothelial cells[9]. In HTS formation, atherosclerosis as well as graft failure the before mentioned changes in immune cell numbers and function and inflammatory mediators lead to altered numbers and function of smooth muscle cells, increased ECM deposition and ultimately thickening of the tissue[7-10]. Coronary chest pain after CABG is termed recurrent angina and is either caused by graft failure (GF) or progression of coronary artery disease (CAD)[9,11]. Chest pain can be identified non-invasively. The aim of this study was to investigate the association between HTS and recurrent angina in an attempt to reveal the possible relation of HTS formation with advanced atherosclerosis and symptomatic graft failure.

Patients and methods

A prospective study on HTS in relation to recurrent angina was conducted. This study is part of a larger observational study, which started in October 2008 and was conducted in the St. Antonius Hospital in Nieuwegein, the Netherlands. The aim of the primary study was to investigate the mechanisms leading to HTS. The St. Antonius Hospital is a major tertiary referral centre for cardiothoracic surgery. Prior to the start of the study, permission was obtained from the Medical Ethics Committee (VCMO) of the St. Antonius Hospital in Nieuwegein, the Netherlands, confirming that the study conformed to the Declaration of Helsinki. All subjects gave written informed consent.

Patients who underwent cardiothoracic surgery via a median sternotomy incision were

included in the primary study. With regard to the CABG procedures, vein grafts consisted of great saphenous vein and were harvested through an open technique and heparinized before being connected to the aorta and coronary arteries. When arterial grafting was performed, the left internal mammary artery was always used, sometimes in combination with a free right internal mammary artery or radial artery graft. Internal mammary arteries were harvested either as a pedicle with concomitant veins or skeletonized. The arteries were heparinized, released distally and prepared with intraluminal papaverine. Patients with pre-existing scars in the anterior thorax area, connective tissue disorders (like Ehlers-Danlos, scleroderma and other disorders associated with abnormal scarring[12]) and patients who were unable to visit the outpatient clinic were excluded from the study. The overall inclusion period lasted from October 2008 to March 2009 and resulted in the inclusion of 120 patients. Of these patients, 31 were not able to complete the follow-up; 25 patients were unable to revisit the clinic for follow-up and six patients diseased. Seventy seven of the 87 patients who completed the follow-up of the primary study had received CABG surgery and were therefore eligible for inclusion in the present study. The sternotomy wound model was selected for this study, because the anterior chest wall is a site of predilection for HTS formation. The surgical procedures were carried out by a small group of cardiothoracic surgeons in a standardized way. Wounds that result from surgical incisions are created under optimal circumstances, such as disinfection, adequate haemostasis and closing of the wound without extreme tension acting on the wound edges.

At four months as well as one year after surgery, patients were seen by the investigators who determined scar type (i.e. (partly) hypertrophic or completely non-hypertrophic). HTS was defined as scar tissue, which is raised at least two millimeters above skin level and confined to the margins of the original wound. Standardized clinical digital photographs were taken after each visit.

A clinical work up with a minimal follow-up period of two years was utilized. Patient information on chest pain and CAD/GF was collected by chart reviews, a questionnaire by telephone and if necessary consultation of general practitioners. Patient characteristics on age, sex, type of CABG (venous, arterial or both), chest pain, use of medication, emergency room visits and the occurrence of cardiac disease or repeat interventions during follow-up were collected. Also, cardiovascular risk factors such as smoking, alcohol use, diabetes mellitus, hypertension, hypercholesterolemia, body mass index (BMI) and physical activity were investigated. The examined patient characteristics are shown in **table 1**. To assess the presence and severity of chest pain the Canadian Cardiovascular Society Functional Classification of Angina (CCS) questionnaire was used[13,14]. Chest pain was subdivided in recurrent angina and non-coronary chest pain. Chest pain with proven ischemic etiology (as diagnosed by means of ECG or stress testing) was named recurrent angina. The remaining forms of chest pain were termed non-coronary chest pain. For determining the physical activity the TNO Nederlandse Norm Gezond Bewegen questionnaire was utilized.

Variable	*NTS (n = 41)*	*HTS (n = 29)*	*p value*
Age (yrs)	67.9 ± 9.9	67.8 ± 9.7	0.991*
Male	34 (83%)	21 (72%)	0.378*
Body mass index (kg/m²)	27.1 ± 3.9	28.8 ± 4.3	0.078£
Alcohol use	25 (61%)	16 (55%)	0.806£
Smoking	6 (15%)	2 (7%)	0.455£
Hypercholesterolemia	16 (39%)	13 (45%)	0.806£
Diabetes mellitus	6 (15%)	8 (28%)	0.230£
Hypertension	22 (54%)	20 (69%)	0.225£
Homocysteinemia	2 (5%)	0 (0%)	0.508£
Physical activity[14]:			0.368#
- Inactive	2 (5%)	2 (7%)	
- Semi-active	5 (12%)	7 (24%)	
- Normally active	34 (83%)	20 (69%)	
Physical fitness[14]:			0.175#
- Not fit	7 (18%)	11 (38%)	
- Semi fit	14 (34%)	7 (24%)	
- Normally fit	20 (49%)	11 (38%)	
Medication:			
- Anticoagulants	41 (100%)	29 (100%)	-
- Lipid lowering	36 (88%)	25 (86%)	1.000£
- Antihypertensive	34 (83%)	27 (93%)	0.289£
- β-blocker	24 (59%)	16 (55%)	0.810£
- ACE-I/ARB	24 (59%)	18 (62%)	0.809£
- Ca antagonist	12 (29%)	10 (35%)	0.794£
- Other	5 (12%)	4 (14%)	1.000£
- Nitroglycerin	4 (14%)	3 (10%)	1.000£
Type of graft:			0.368#
- Venous	7 (17%)	9 (31%)	
- Arterial	7 (17%)	5 (17%)	
- Combination	27 (66%)	15 (52%)	
Follow-up (months)	26.2 ± 1.0	26.4 ± 1.0	0.347*

Table 1: patient characteristics *Data are presented as number (percentage) or mean ± SD. NTS = normotrophic scar, HTS = hypertrophic scar, ACE-I/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker, Ca antagonist = calcium channel antagonist, * = T-test, # = Chi-square, £ = Fisher's exact.*

This validated Dutch questionnaire classifies patients into normal active, semi-active or

non-active and normal-fit, semi-fit and non-fit groups in order to determine physical activity and fitness, respectively[15]. The study population was divided into two groups according to the presence or absence of HTS.

The primary endpoint was the incidence of recurrent angina. Secondary endpoints were myocardial infarction, GF found with coronary angiography and repeat revascularization during follow-up.

Statistical analyses were performed using SPSS (version 15.0.1 for Windows). Data are expressed as numbers and percentages for categorical outcomes and as means ± standard deviations for continuous outcomes. To assess the significance of differences between categorical outcomes the Chi-square and Fisher's exact test were applied. Independent samples T-test was used to compare continuous outcomes. Results with a p value < 0.05 were considered significant.

Variable	*NTS (n = 41)*	*HTS (n = 29)*	*p value*
Chest pain	7 (17%)	11 (38%)	0.058£
CCS-score:			0.250#
- Class 1	34 (83%)	22 (76%)	
- Class 2	3 (7%)	6 (21%)	
- Class 3	0 (0%)	0 (0%)	
- Class 4	4 (9.8%)	1 (3%)	
ER visit	10 (24%)	9 (31%)	0.592£
Diagnosis:			
- Recurrent angina	2 (5%)	5 (17%)	0.180£
- Myocardial infarction	2 (5%)	0 (0%)	0.508£
Intervention after CABG	3 (7%)	2 (7%)	1.000£
- CAG	2 (5%)	2 (7%)	1.000£
- PCI/coronary stent	1 (2%)	0 (0%)	1.000£
Graft occlusion at CAG	1 (2%)	0 (0%)	1.000£

Table 2: results *Data are presented as number (percentage). Chest pain = coronary and non-coronary chest pain, CCS = Canadian Cardiovascular Society Functional Classification of Angina, ER = emergency room, CABG = Coronary Artery Bypass Grafting, CAG = coronary angiography, PCI = percutaneous Coronary Intervention, # = Chi-square, £ = Fisher's exact.*

Results

Seventy seven of the 87 patients who completed the follow-up of the primary study had received CABG surgery and were therefore eligible for inclusion in the present study. Seven patients could not be included: six of them could not be contacted and one patient deceased

during follow-up due to metastasized malignant disease. Therefore, the final study population consisted of 70 patients (55 men, 15 women; mean age 67.8 ± 9.8 years), which were observed during a mean follow-up of 26 months (range: 25-29) after CABG surgery.

In the study population, HTS was observed in 29 patients (41%). The two patient groups were comparable with regard to their baseline characteristics on medications taken after CABG, demographic and cardiovascular risk factors and type of graft (**table 1**).

None of the patients reported chest pain at one year post-CABG, whereas 18 patients suffered from chest pain after two years. The results on endpoint variables two years after CABG are shown in **table 2**. Recurrent angina occurred in five patients with HTS compared to two patients with normal scars ($p = 0.180$). The CCS scores were comparable between groups ($p = 0.25$) as was the prevalence of non-coronary chest pain ($p = 0.38$). Coronary angiography was performed in two patients with HTS and in three patients with normal scars. One of these patients had developed graft failure. This patient had a normal scar.

Discussion

In this study population of 70 CABG patients, no significant association between hypertrophic scar formation (HTS) and recurrent angina was found.

Recurrent angina (chest pain after CABG) is either the result of graft failure (GF) or progression of coronary atherosclerosis/coronary artery disease (CAD)[8,9,11]. GF occurring two years after CABG (mid-term occlusion) is mainly caused by intima hyperplasia. The foundation of these processes lies in several abnormalities which consist of excessive secretion of pro-inflammatory cytokines, increased influx of inflammatory cells and consequently excessive accumulation of extracellular matrix resulting in thickening of the tissue (fibrosis)[9]. The same aberrations of wound healing have been observed in HTS formation[1,3,4,7].

Since the abnormal wound healing processes in HTS resemble those in CAD/GF, these forms of excessive fibrosis are possibly related. However, an association of HTS with CAD/GF could not be demonstrated in this study. First, recurrent angina, which is related with CAD/GF, was not associated with HTS. Second, objective proof of CAD/GF in the form of coronary angiography was available for only one patient since coronary angiography was not used as a standard diagnostic tool in this study. Consequently, the number of asymptomatic stenoses may have been underestimated in the present study. Several clinicians did observe an association between HTS and trachea stenosis[16,17]. Maybe this process occurs solely in tissues originating from the ectoderm (the primary germ cell layer which gives rise to the skin) such as the trachea. Blood vessels arise from the mesoderm. This different origin might explain the absence of a correlation between HTS and CAD/GF.

In this study, the CCS questionnaire was not predictive for the occurrence of recurrent angina, which is in line with current literature[14,18,19]. The prevalence of HTS was 41%, which corresponds to literature as well[1,2]. In contrast, the prevalence of proven GF in the study population, diagnosed by coronary angiography, was 1.4%. This is low compared to previous reports on incidence of GF. According to a large retrospective study of Javaid and colleagues symptomatic GF occurs in almost 6% of patients 12 months post-CABG[20]. Boudriot and colleagues examined the majority of their research population by angigraphy one year after CABG. They reported a prevalence of 21% graft occlusions, most of which were asymptomatic[21]. In a larger study, Goldman and colleagues noticed GF in 5-16% after one year and 7-20% after three years, as determined by angiography[22]. The relatively low prevalence of proven graft occlusion in the present study can be explained by the observational design of the study. Only a minority of patients (7.1%), who were suspected for GF because of cardiac symptoms, underwent coronary angiographies.

In conclusion, this prospective study did not identify an association between the occurrence of HTS and recurrent angina after CABG. Recommendations for future studies to determine the association between HTS and recurrent angina resulting from CAD/GF include the use of larger groups in which all of the patients undergo coronary angiographies. This will increase the reliability of the results and consequently statistical power.

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