International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Predictive value of Type D personality for impaired endothelial function in patients with coronary artery disease

Johan Denollet [a,b,*], Romy A. van Felius [a], Paul Lodder [a], Paula M. Mommersteeg [a], Inge Goovaerts [b], Nadine Possemiers [b], Luc Vanhees [c], Paul Beckers [b], Nele Pattyn [c], Emeline M. Van Craenenbroeck [b]

[a] CoRPS - Center of Research on Psychology in Somatic Diseases, Tilburg University, The Netherlands
[b] Department of Cardiology, University Hospital Antwerp, Antwerp, Belgium
[c] Department of Rehabilitation Sciences, Katholieke Universiteit Leuven, Heverlee, Belgium

ARTICLE INFO

Article history:
Received 16 December 2017
Received in revised form 10 February 2018
Accepted 15 February 2018
Available online xxxx

Keywords:
Coronary artery disease
Endothelial dysfunction
FMD
Type D personality
Depression

ABSTRACT

Background: Type D personality (high negative affectivity and social inhibition) is associated with cardiovascular events and coronary plaque severity. Whether Type D is also related to functional vasomotion abnormalities is unknown. We examined concurrent and predictive associations of Type D with endothelial dysfunction in patients with coronary artery disease (CAD).
Methods: At baseline, 180 CAD patients (90% men; M = 58.0 years) completed Type D (DS14) and depression scales, and entered a 12-week exercise program. Flow-mediated dilation (FMD) of the brachial artery and circulating $CD34^{+}/KDR^{+}/CD45^{+}_{dim}$ endothelial progenitor cells (EPCs) were assessed at baseline, 3 months, and 12 months. Logistic regression and linear mixed models were used to analyze endothelial function.
Results: Type D personality was associated with decreased FMD across baseline, 3 months, and 12 months (mixed model analysis, p = 0.04), after adjustment for clinical characteristics, exercise training and depression. There was no significant association between Type D and decreased EPCs (p = 0.07). Age and smoking were other significant correlates of FMD and EPCs. Using a FMD <5.5% cut-off, Type D patients more often had endothelial dysfunction at baseline (24/37 = 65%) than non-Type Ds (63/143 = 44%); OR = 3.03, 95% CI 1.04–8.80. This significant Type D effect was confirmed in prospective analyses of endothelial dysfunction at 12 months (OR = 3.43, 95% CI 1.01–11.64), and in subgroup analyses of male patients.
Conclusions: Type D personality was associated with impaired endothelial function in men with CAD. This association was robust across time, independent from depressive symptoms, and supports the notion that Type D has an adverse effect on cardiovascular health in patients with CAD.

1. Introduction

Despite major advances in treatment, patients with coronary artery disease (CAD) continue to suffer cardiac events [1] that can also be stress-related. Patients with Type D (*distressed*) personality are prone to stress [2]; i.e., they tend to experience negative emotions (negative affectivity) and inhibit self-expression (social inhibition). Type D is related to adverse events in cardiac patients [2], and the European Society of Cardiology [3] and its cardiac rehabilitation section [4] have included Type D as a psychosocial risk marker. Yet, some studies found no effect of Type D on all-cause mortality [5]. A meta-analysis showed that Type D predicted a 2-fold increased risk of cardiac events [6], but also indicated heterogeneity among studies.

This heterogeneity relates to the biological plausibility of Type D [7]. Re-analysis of studies on CAD showed that Type D predicted cardiac events/death but not non-cardiac death [8]. Hence, Type D may be related to specific cardiovascular pathways [7]. Type D is related to increased coronary plaque severity [9,10] but its role in functional coronary abnormalities is unknown. Endothelial cells regulate vascular and inflammatory responses, and endothelial dysfunction induces functional coronary abnormalities that play a key role in the development of CAD [11,12]. Flow-mediated dilation (FMD) is a measure of endothelial function that reflects vasodilation through release of nitric oxide in response to a hyperemia-induced increase in endothelial shear stress [13,14]. FMD of the brachial artery is related to coronary endothelial dysfunction [12], and has a strong prognostic value in predicting cardiovascular events [15].

Acute [16,17] and chronic [18,19] stress can lead to endothelial dysfunction. Type D individuals [2] report more stress but it is unclear whether Type D is directly related to endothelial function. Type D predicted poor FMD in patients with lung disease [20] while studies in

* Corresponding author at: CoRPS, Department of Medical and Clinical Psychology, Tilburg University, P.O. Box 90153, 5000 LE Tilburg, The Netherlands.
E-mail address: J.Denollet@tilburguniversity.edu (J. Denollet).

https://doi.org/10.1016/j.ijcard.2018.02.064
0167-5273/

healthy subjects found mixed results [21,22]. Type D was also related to biomarkers of endothelial activation [23]. Type D might contribute to endothelial dysfunction through different candidate pathways. Increases in superoxide anions formation [24], oxidative stress [25], TNF-α [26], and cortisol [27] have been observed in Type D individuals, and may induce endothelial dysfunction [1,12,13,28].

Therefore, our aim was to examine the predictive value of Type D for endothelial dysfunction in CAD. We also examined the link between Type D and endothelial progenitor cells (EPC) as marker of endothelial repair [13]. Because endothelial dysfunction [29,30] and the effect of Type D on cardiovascular stress [31] may occur more in men than in women, we also wanted to study Type D and endothelial dysfunction among men in particular. Diabetes, hypertension, smoking and depression are associated with Type D [23,32–34] and were included as covariates.

2. Methods

2.1. Study design and participants

Patients from the Study on Aerobic INTerval EXercise training in CAD (SAINTEX-CAD) were included at the Antwerp University Hospital (n = 100) or Leuven University Hospital (n = 100) in Belgium. Rationale and methodology of this prospective trial are described elsewhere [35]. In brief, 200 patients (90% men; m = 58.4 ± 9.1y) were randomized to a supervised 12-week exercise program of aerobic *interval* or *continuous* training. Inclusion criteria were: 1) angio-graphically documented CAD (stenosis ≥75% in any branch) or acute myocardial infarction (AMI), 2) left ventricular ejection fraction (LVEF) >40%, 3) on optimal medical treatment, 4) stable regarding symptoms and medication for at least 4 weeks, and 5) included between 4 and 12 weeks following AMI, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) [35,36].

Patients underwent assessment of endothelial function by FMD and blood sampling for quantification of EPCs at baseline, after 3 months, and after 12 months. Blood sampling was performed in the morning, in fasting conditions and patients refrained from exercise at least 8 h before the measurements. Flow cytometric analyses were performed in the Antwerp Laboratory of Cellular and Molecular Cardiology that served as the core laboratory [36]. The SAINTEX-CAD trial complied with the World Medical Association Declaration of Helsinki on ethics in medical research. The study was approved by the local ethics committees of both participating hospitals, and all participants gave written informed consent [35].

2.2. Type D personality and depressive symptoms

Personality was assessed at baseline with the 14-item Type D Scale (DS14) [32]. The DS14 comprises two 7-item measures; negative affectivity (NA) and social inhibition (SI). Items are rated on a 5-point scale ranging from 0 = false to 4 = true. A cut-off ≥10 on the NA and SI measures identifies individuals with elevated trait levels, and individuals with a score ≥10 on both scales are categorized as Type D [32–34]. The NA and SI scales are uni-dimensional and internally consistent (Cronbach's α = 0.88 and 0.86), and have good test-retest reliability [32].

To compare the separate and combined effects of high and low trait levels, the cut-off ≥10 was used to define four distinct personality subgroups [33]; i.e., low on both traits (NA ≤ 9 and SI ≤ 9; reference group), SI only (SI ≥ 10 but NA ≤ 9), NA only (NA ≥ 10 but SI ≤ 9), and Type D (NA ≥ 10 and SI ≥ 10). Previously, we showed that this classification scheme was successful in predicting prognosis in CAD patients, and that Type D was associated with adverse cardiac events while patients of the NA only or SI only subgroups were not at increased risk [8,33].

The Dutch 7-item depression measure [37] of the Hospital Anxiety and Depression Scale was used to assess depressive symptoms and control for these symptoms in statistical analyses. The 7 items are rated on 4-point scale (0–3), and the total score ranges between 0 and 21.

2.3. FMD assessment of endothelial function

Endothelial function was assessed by FMD of the brachial artery [36]. Ultrasound scanning was used to measure endothelium-dependent vasodilation in response to reactive hyperemia [14]. To control environmental factors that could influence FMD assessment, all analyses were performed in the morning, in fasting conditions and in a quiet temperature-controlled room (21–24 °C) by a trained operator that was blinded for the study intervention. Subjects refrained from exercise, food and caffeine at least 8 h before the measurements. Patients were in supine position and the brachial artery was imaged above the antecubital fossa. Blood pressure was obtained after 10 min of rest with an automated blood pressure monitor (Omron M6). The forearm was occluded during 5 min with a cuff placed on the forearm distal to the brachial artery, at a cut-off pressure of at least 200 mm Hg or 60 mm Hg supra-systolic. Images were continuously recorded from 1 min before cuff inflation to 3 min after cuff deflation and were analyzed using edge-detection software FMD-i by Flomedi (Brussels, Belgium). FMD was expressed as the percentage change in diameter of the brachial artery [14]. Measurements were performed by two experienced investigators and analyses of the measurements were blinded to the treatment allocation and study visits.

2.4. Clinically relevant endothelial dysfunction

In addition to analyzing continuous FMD values, we also examined impairment in endothelial function in both concurrent (baseline) and prospective (12 months) analyses. There is a wide variability in FMD levels across studies [38], and a lack of consensus for a clinical relevant cut-off value [14]. In a study of patients with CAD, impaired FMD as defined by a cut-off <5.5% predicted an increased risk of adverse cardiovascular events [39]. In our study, the median value of FMD was 5.6% and 6.1% at baseline and 12 months. This corresponds well to the median of 5.2% reported in a meta-analysis of 16 studies [38] and to the cut-off <5.5% that has been related to poor prognosis in CAD [39]. Therefore, we used the FMD <5.5% cut-off to define clinically relevant endothelial dysfunction both at baseline and 12 months follow-up.

2.5. Assessment of circulating EPCs

Circulating EPC numbers, defined as $CD34^+/KDR^+/CD45^+$dim cells, were quantified by multi-parametric flow cytometry [36]. Whole blood was fixed (TransFix, Caltag Medsystems, Buckingham, UK) and processed 2 to 3 days after sampling. After pretreatment with Fc receptor blocking reagent (Miltenyi Biotec, Bergisch Gladbach, Germany), samples were incubated with CD34-PE-Cy7 (BD Pharmingen, Erembodegem, Belgium), KDR-APC (R&D Systems, Minnesota), and CD45-APC-H7 (BD Pharmingen) antibodies. Addition of the nucleic acid dye SYTO 13 (Life Technologies, Ghent, Belgium) allowed identification of non-nucleated cells and cellular debris. At least one million total events were recorded on a FACSCanto II flow cytometer (Becton Dickinson, New Jersey). Fluorescence-minus-one samples and unstained samples served as negative controls. Numbers of EPCs were analyzed using FACSDiva software (Becton Dickinson, version 6.1.2) and expressed as cells per million $CD45^+$ mononuclear cells with low forward (FSC) and side scatter (SSC) [36].

2.6. Statistical analyses

One-way analyses of variance and chi-square tests were used to examine differences in continuous and categorical baseline variables as a function of personality. Two separate linear mixed models were used to assess the association of the different personality profiles with FMD and EPC markers of endothelial function across 3 time points (baseline, 3 months, 12 months). In the linear mixed model analyses, all three time points were included and modeled according to an unstructured covariance matrix. Demographics (age, sex), exercise treatment (interval or continuous training), standard cardiovascular risk factors (hypertension, diabetes, smoking), and depressive symptoms were included as covariates in these analyses. Next, we used multiple logistic regression models to assess the concurrent (baseline) and prospective (12 months) relationships between personality profiles and endothelial dysfunction as defined by the FMD cut-off <5.5% [39]. These models included the covariates mentioned above. Logistic regression models of endothelial dysfunction were replicated in the group of men with CAD. All statistical analyses were performed using SPSS 24.0 for Mac and SPSS 22.0 for Windows (IBM SPSS Statistics for Windows, Armonk, NY). All tests were 2-tailed, and p-values <0.05 were considered to be statistically significant.

3. Results

3.1. Baseline characteristics

For 12 of the 200 participants, personality assessment was missing; Table 1 presents the characteristics of the 188 patients included in this study. The mean age was 58.0 years, 90% were men, 60% had survived an AMI, and the large majority of patients underwent PCI or CABG. Based on the standard cut-off ≥10 on the NA and SI measures of the DS14 [32], 39 patients (21%) were classified as Type D personality, 29 (15%) as NA only, 37 (20%) as SI only, and 83 (44%) as the reference group with low scores on both traits. Type D personality was not significantly related to age, sex, diagnosis of an index AMI, invasive treatment with CABG or PCI, hypertension, diabetes, smoking or medication use (statins, acetylsalicylic acids, beta-blockers, angiotensin-converting enzyme inhibitors, anti-diabetic medication, diuretics, nitrates). However, patients with Type D personality displayed significantly higher levels of depressive symptoms than non-Type D patients did (Table 1).

3.2. FMD and EPC measures of endothelial function

Mean scores (±standard deviation) of FMD were 5.61 ± 2.83, 6.68 ± 2.97 and 6.29 ± 3.22 at baseline, 3 months and 12 months. FMD was missing for 8, 30, and 45 patients at these 3 time points. Median

Please cite this article as: J. Denollet, et al., Predictive value of Type D personality for impaired endothelial function in patients with coronary artery disease, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.02.064