ORIGINAL INVESTIGATION

Heritability of chronic venous disease

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Abstract Varicose veins without skin changes have a
prevalence of approximately 20% in Northern and Western
Europe whereas advanced chronic venous insufficiency
affects about 3% of the population. Genetic risk factors are
thought to play an important role in the aetiology of both
these chronic venous diseases (CVD). We evaluated the
relative genetic and environmental impact upon CVD risk by
estimating the heritability of the disease in 4,033 nuclear
families, comprising 16,434 individuals from all over Ger-
many. Upon clinical examination, patients were classified
according to the CEAP guidelines as either C2 (simple vari-
cose veins), C3 (oedema), C4 (skin changes without ulcer-
ation), C5 (healed ulceration), or C6 (active ulcers). The
narrow-sense heritability (h^2) of CVD equals 17.3% (stan-
dard error 2.5%, likelihood ratio test $P = 1.4 \times 10^{-13}$). The
proportion of disease risk attributable to age (at ascertain-
ment) and sex, the two main risk factors for CVD, was
estimated as 10.7% (Kullback–Leibler deviance R^2). The
heritability of CVD is high, thereby suggesting a notable
genetic component in the aetiology of the disease. System-
atic population-based searches for CVD susceptibility genes
are therefore warranted.

Background

Chronic venous disease (CVD) is one of the most common
disorders in Northern and Western Europe. According to
the CEAP classification, CVD comprises those clinical
entities that are characterized by visible venous ecstasies
but which are not associated with an identifiable mecha-
nism of venous dysfunction (Porter and Moneta 1995;
Kistner et al. 1996). The clinical presentation of CVD
ranges from complication-free telangiectasias or reticular
veins, via varicose veins (VV) without oedema and skin
changes, to venous ulceration. Varicose veins requiring
medical care but lacking signs of oedema or skin changes
are sometimes referred to as 'simple VV' and have been
given CEAP classification C2. If skin changes or ulcer-
ations occur, patients are defined as having 'chronic vein
insufficiency' (CVI), classified as CEAP C3 to C6 (Ruck-
ley et al. 2002). Defined in this way, CVD represents a
summary term comprising patients with either simple VV
or CVI (Eklof et al. 2004, 2009). Epidemiological studies
of CVD have revealed that VV affects 16–46% of females
and 12–40% of males (Evans et al. 1999; Rabe et al. 2003;
Carpentier et al. 2004). The prevalence of CVI ranges from
5 to 18% in females, and from 7 to 15% in males (Evans
et al. 1999; Rabe et al. 2003; Carpentier et al. 2004).

Although CVD is relatively common, the aetiologic
factors predisposing individuals to the dilatation, elonga-
tion and tortuosity of the saphenous vein and its tributaries
are still poorly understood. The clinically observed thick-
ening of the vessel wall appears to be associated with an

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increase of thick and disorganized collagen bundles (Sansilvestri-Morel et al. 2007). In addition to age, sex and obesity, family history was also found to be a major risk factor for CVD (Coon et al. 1973; Abramson et al. 1981; Brand et al. 1988; Franks et al. 1992; Sisto et al. 1995; De Backer 1997). However, family data were often inconsistent and confounded by selection bias (Meissner 2004). A CVD twin study reported 84% phenotypic concordance between monozygotic twins, compared to only 39% between dizygotic twins (Niermann 1964). In view of these ambiguities, we set out to formally assess the heritability of CVD in a large sample of affected nuclear families from all over Germany.

Materials and methods

Between October 2005 and July 2008, a total of 2,701 index patients with CVD were recruited at the Capio Mosel-Eifel-Clinic (Capio MEC, Bad Bertrich, Germany), which is specialized in the treatment of severe forms of CVD. The ethics committee of the Kiel medical faculty and the local data protection authorities both approved the study. Written informed consent was obtained from all participants. Exclusion criteria were clinically overt debility, any signs of acute deep vein thrombosis and congenital causes of CVD. All patients suffered from severe injury of their great saphenous vein and had stayed in the clinic for at least 4 days.

A questionnaire was administered to each index patient by Capio MEC staff to obtain information on their demographic and personal characteristics (sex, date and place of birth, parental origin) as well as their medical history (medical treatment, pain, severe operations, age at CVD onset, presence of deep vein thrombosis, phlebitis). Duration of disease (in years) was calculated from these data as the difference between age at ascertainment and age at onset. A 30-ml blood sample for further genetic analysis, including candidate gene and genome wide association studies, was taken by Capio MEC staff and immediately frozen at −20°C. Genomic DNA was prepared from defrosted blood samples using the Invisorb Blood Giga Kit (Invitec, Berlin, Germany). All DNA samples were quality-checked on agarose gels. Patients were also interviewed about the CVD status of all living first degree relatives (parents and siblings). Family information was provided by all 2,701 index patients, which generated 4,033 nuclear families comprising 16,434 individuals for heritability analysis (Table 1).

All index patients were classified according to the severity, cause, site and specific abnormalities of their disease, using the CEAP classification. The CEAP classification was developed in 1994 by an international ad hoc committee of the American Venous Forum, endorsed by

Table 1 Data base for the estimation of narrow-sense heritability h^2

CEAP grade	No. pedigrees	No. nuclear families	No. individuals
Any (CVD)	2,701	4,033	16,434
C2 (VV)	448	662	2,706
C3	1,698	2,539	10,317
C4	441	656	2,702
C5&C6	114	174	701
C3 to C6 (CVI)	2,253	3,369	13,720
C2 to C4	2,587	3,857	15,725

the Society for Vascular Surgery and incorporated into the 'Reporting Standards in Venous Disease' in 1995 (Porter and Moneta 1995; Kistner et al. 1996). The CEAP classification underwent its first official review and revision by an international panel under the auspices of the American Venous Forum in 2004 by Eklof et al. (2004). Its key elements are Clinical severity, Etiology or cause, Anatomy and Pathophysiology.

Clinical severity was the most important criterion for the initial assessment of index patients in our study. There are seven grades of increasing clinical severity of CVD: C0, no evidence for venous disease; C1, superficial spider veins; C2, simple VV; C3, oedema of venous origin; C4, skin changes ascribed to venous disease (e.g. pigmentation, venous eczema and lipodermatosclerosis); C5, skin changes as defined above, with healed ulceration; C6, skin changes, as defined above, with active ulceration. Groups C5 and C6 were combined in our study ('C5&C6') because of the limited number ($n = 114$) of samples available (Table 1). Patients of grades C3 to C6 show an increasing severity of CVI, and all suffer from a functional abnormality of the venous system. For estimating heritability (Fisher 1918) CVD status ('affected', 'non-affected'), current age and sex were recorded for all first degree relatives. It should be noted that, so far, only a few prevalence studies have used the CEAP classification as a phenotypic measure (Rabe et al. 2003; Carpentier et al. 2004).

Preoperative diagnostic tests entering into the CEAP grading of index patients included handheld Doppler evaluation of the great and small saphenous veins as well as venous duplex ultrasonography. In combining B mode imaging with pulsed Doppler, duplex is capable of accurately localizing both the venous obstruction and the valvular reflux to specify venous segments. Colour duplex imaging was performed with a Hewlett Packard Image Point HX, employing a 7.5 MHz probe. Examinations were undertaken with the patient in a standing position, using the valsalva manoeuvre and manual calf compression. A reflux >2 s was considered clinically significant. For estimating the actual length of clinically significant reflux, the handheld Doppler and the colour duplex imagine were

combined with photoplethysmography to gauge the venous hemodynamics. Repeating the test while firmly compressing a particular vein allows assessment of the degree of hemodynamic disturbance contributed by that vein. Specifically, if the venous refilling time increases from 10 s (15) to >25 s when the vein is compressed, this vein can be assumed to contribute sizeably to the patients health problem (Meissner 2004).

The genetic contribution to CVD was assessed by estimating the heritability of the disease using a pedigree-based likelihood approach as implemented in the SOLAR software package (Almasy and Blangero 1998). A total of 2,701 pedigrees comprising the index patient and the self-reported disease status of their first degree relatives (parents and siblings) were used for analysis. The narrow-sense heritability, h^2, is defined as the proportion V_A of the phenotypic variance V_P in a population that is attributable to additive genetic causes, i.e., $h^2 = V_A/V_P$ (Visscher et al. 2008). A 95% confidence interval for h^2 was derived as ± 2 standard errors of the estimate. The statistical significance of h^2 was assessed by means of a likelihood ratio test (Guerra et al. 1999). The influence of the two main CVD risk factors, namely sex and age, upon CEAP grade was estimated using the Kullback–Leibler deviance R^2. The h^2 values of individual CEAP grades or grade ranges (Tables 1, 2) were estimated grouping index patients into six subgroups, namely C2, C3, C4, C5&C6, C3 to C6 (CVI) and C2 to C4 (samples without any past or acute venous ulcer). Sex differences in terms of ascertainment age, age at CVD onset, disease duration or BMI were assessed for statistical significance using a Welch t test for unpaired samples. Two-factor analysis of variance was carried out to evaluate the joint influence of sex and CEAP grades on BMI. All statistical analyses were done by using R version 2.8.1 (http://www.R-project.org).

Results

We recruited 2,701 patients (1,904 females, 797 males), which represented approximately 90% of the total number

of patients treated at Capio MEC between October 2005 and July 2008 (Table 3). Simple VV (CEAP grade C2) was diagnosed in 448 (16.6%) of the patients (13.0% of males, 18.1% of females). In total, 2,253 (83.4%) of the index patients were affected by CVI (CEAP grade C3 to C6), the majority having either grade C3 (62.8%) or grade C4 (16.3%). Only 4.2% were affected by grades C5 and C6 (Table 3). Males were more severely affected (C4 27.4%, C5&C6 5.5%) than females (C4 11.7%, C5&C6 3.7%). Heritability estimation was carried out in 4,033 nuclear families from 2,701 pedigrees, comprising a total of 16,434 individuals (Table 1), with family sizes varying between 3 and 14 individuals. The h^2 estimate for overall CVD was $17.3 \pm 2.5\%$ ($P = 1.4 \times 10^{-13}$; Table 2). For grade C2 alone, h^2 was $18.5 \pm 6.0\%$ ($P = 7.3 \times 10^{-4}$) whereas h^2 equalled $17.1 \pm 2.2\%$ ($P = 2.0 \times 10^{-49}$) for the CVI phenotype (grades C3 to C6). The grade-specific estimates of h^2 were as follows: $9.2 \pm 11.3\%$ for C5&C6 ($P = 0.192$, not significant), $18.3 \pm 2.1\%$ for C3 ($P = 1.5 \times 10^{-9}$) and $16.7 \pm 6.0\%$ for C4 ($P = 1.2 \times 10^{-3}$). Using age (at blood donation) and sex as covariates, the Kullback–Leibler deviance R^2 was estimated to be 10.7% ($P = 4.6 \times 10^{-9}$). A notably smaller Kullback–Leibler R^2 was only observed for C5&C6 grades (3.5%).

The mean ascertainment age of our patients was 56.2 years [standard deviation (SD) 11.1 years, range 18–83 years; Table 4]. No significant age difference was observed between the two sexes. The overall mean age at CVD onset was 32.6 years (SD 12.2, range 5–72), with 36.8 years (SD 12.8, range 5–72) for males and 30.8 years (SD 11.3, range 6–72) for females (Table 4). The grade-specific mean age of onset ranged from 30.7 years (SD 10.8) for C5&C6 to 35.8 years (SD 11.6) for C2 whereas the grade-specific mean age at ascertainment of our patients ranged from 52.0 years (SD 12.3) for C2 to 60.9 years (SD 10.4) for C5&C6 (Table 5). The mean disease duration was 23.4 years (SD 12.9, range 0–63) for all index patients combined, 19.3 years (SD 12.7, range 0–55) for males, and 25.1 years (SD 12.9, range 0–63) for females (Table 4). The grade-specific mean of the disease duration ranged from 20.1 years (SD 12.8 years) for grade

Table 2 Estimates of the narrow-sense heritability (h^2) for different CEAP grades

CEAP grade	h^2 (%)	Standard error (%)	P value[a]	Kullback–Leibler Deviance R^2 (%)
Any (CVD)	17.3	2.5	1.4×10^{-13}	10.7
C2 (VV)	18.5	6.0	7.3×10^{-4}	12.2
C3	18.3	2.1	1.5×10^{-9}	11.8
C4	16.7	6.0	1.2×10^{-3}	8.5
C5&C6	9.2	11.3	0.192	3.5
C3 to C6 (CVI)	17.1	2.2	2.0×10^{-49}	10.4
C2 to C4	17.6	2.3	2.2×10^{-13}	11.0

[a] Likelihood ratio test for $h^2 = 0$, adjusted for age and sex

Table 3 Prevalence of different CEAP grades in the study population

CEAP grade	Total ($n = 2,701$)	Males ($n = 797$, 29.5%)	Females ($n = 1,904$, 70.5%)
C2 (VV)	448 (16.6%)	104 (13%)	344 (18.1%)
C3	1,698 (62.8%)	431 (54.1%)	1,267 (66.5%)
C4	441 (16.3%)	218 (27.4%)	223 (11.7%)
C5&C6	114 (4.2%)	44 (5.5%)	70 (3.7)
C3 to C6 (CVI)	2,253 (83.4%)	693 (87%)	1,560 (81.9)
C2 to C4	2,587 (95.7%)	753 (94.5%)	1,834 (96.3%)

VV varicose veins, *CVI* chronic venous insufficiency

Table 4 Characteristics of CVD patients

	All patients ($n = 2,701$)	SD (range)	Males ($n = 797$)	SD (range)	Females ($n = 1,904$)	SD (range)	P value
Age at ascertainment	56.2 years	11.1 years (18–83)	56.2 years	11.6 years (18–81)	56.1 years	11.9 years (21–83)	0.95 (not significant)
Age at onset	32.6 years	12.2 years (5–72)	36.8 years	12.8 years (6–72)	30.8 years	11.3 years (5–72)	2.2×10^{-16}
Disease age	23.4	12.9 years (0–63)	19.3 years	12.7 years (0–55)	25.1 years	12.9 years (0–63)	2.2×10^{-16}
BMI	26.8	4.7 (14–66)	27.5	3.7 (20–53)	26.6	5.0 (14–66)	9.2×10^{-7}

Given are the overall and sex-specific means, standard deviations (SD) and ranges

Table 5 CEAP grade-specific characteristics of CVD patients

CEAP grade	Age at onset	Age at ascertainment	Disease age	BMI
C2 (VV)	35.8 (11.6, 5–72)	52.0 (12.3, 18–82)	20.1 (12.8, 0–54)	25.6 (4.5, 20–42)
C3	32.9 (12.1, 6–72)	56.4 (10.6, 23–82)	23.4 (12.6, 0–63)	26.5 (4.5, 14–66)
C4	33.2 (12.7, 10–72)	58.3 (10.5, 24–81)	25.3 (13.0, 1–56)	28.3 (4.8, 18–46)
C5&C6	30.7 (10.8, 14–71)	60.9 (10.4, 33–83)	29.8 (13.0, 6–61)	29.6 (5.2, 21–45)
C3 to C6 (CVI)	32.8 (12, 6–72)	57 (10.6, 23–83)	24.1 (12.8, 0–63)	27.1 (4.7, 14–66)
C2 to C4	32.8 (12.1, 5–72)	55.9 (11.1, 18–82)	23.2 (12.8, 0–63)	26.7 (4.6, 14–66)

Given are the means and, in brackets, standard deviations and ranges

C2 to 29.8 years (SD 13.0 years) for grade C5&C6 (Table 5). The mean BMI was 26.8 (SD 4.7, range 14–66) for all index patients combined, and equalled 27.5 (SD 3.7, range 20–53) for males and 26.6 (SD 5.0, range 14–66) for females (Table 4). The grade-specific BMI ranged from 25.6 (SD 4.5) for C2 to 29.6 (SD 5.2) for C5&C6 (Table 5).

Discussion

The major aim of the present study was to determine the heritability of CVD and to assess the relative impact of genetic (familial background, sex) and non-genetic factors (age, BMI) upon CVD risk. Data from a large number of individual index patients and the disease status, age and sex of their first degree relatives led us to conclude that the additive genetic component of CVD is approximately 17%.

Two recently published, population-based studies of CVD also used the CEAP classification to define the disease phenotype (Rabe et al. 2003; Carpentier et al. 2004). However, these studies employed a substantially different recruitment scheme than ours. The Bonn Vein Study for example, included all CEAP grades thereby addressing a much lower proportion of severe CVI cases than we did (Rabe et al. 2003). In line with the Bonn Vein Study (Rabe et al. 2003), however, males in our study were found to be more often affected by the severe CEAP grades C4 to C6 phenotypes than females.

Interestingly, h^2 was found to vary only little with disease severity (from 18.5% for C2 to 16.7% for C4; Table 5). Although not formally statistically significant ($P = 0.192$, Table 2), the substantially lower h^2 estimate obtained for grades C5&C6 (9.2%) may indicate a smaller genetic impact upon the severe CVD phenotype, since the number of samples in this category was comparatively small ($n = 114$), however, small h^2 estimate obtained may also reflect higher sampling variance. Therefore, further studies specifically targeted at severe grades C5&C6 appear warranted.

The main CVD risk factors identified so far have been age (at ascertainment), female sex and familial history (Rabe et al. 2003), and our study was the first to include age at disease onset and the disease duration disease as well. Index patients with simple VV (C2) were ascertained at a mean age of 52 years whereas those with a more severe form of CVI were ascertained at a mean age of 60.9 years. These results corroborate an earlier multicenter study by Carpentier (2004), which also revealed a statistically significant association between a higher CEAP grade and an older current age of patients. However, an inverse relationship was observed in our study between disease severity and the age at disease onset. Patients affected by simple VV (C2) were first affected at 35.8 years compared to 30.7 years for patients with CVI (C3 to C5&C6). This discrepancy may be explicable in terms of the CVI phenotype requiring a longer time period for its etiopathology than VV. Indeed, CVD is a progressive disease where those with longer disease duration (i.e., earlier onset and/or older current age) can be expected to show the worst phenotype. Consequently, a remarkable increase in disease duration with disease severity was observed in our study, ranging from 20.1 years for C2, via 23.4 years and 25.3 years for C3 and C4, respectively, to 29.8 years for C5&C6.

In most studies undertaken so far, CVD has been found to be more prevalent among women than among men (Rabe et al. 2003), although this difference was only small in a recent study by Labropoulos (2003). Among our samples, twice as many patients were female ($n = 1{,}904$, 70.5%) than male ($n = 797$, 29.5%) thereby highlighting the CVD-predisposing role of the female sex (Table 3). The reasons for the observed sex difference may be manifold. Clearly, women are more likely to seek medical attention for varicose veins and are about three times more likely to undergo treatment (Madar et al. 1986). However, a remarkable sex difference was also observed in our data in terms of the mean age at disease onset, with females showing first symptoms of CVD at 30.8 years of age, compared to 36.8 years for males (Table 4), and in terms of disease duration (19.3 years for males, 25.1 years for females). The higher proportion of female CVD patients consistently noted in previous reports, may thus be at least partially explicable by a different timing of disease in the two sexes.

Obesity has been noted to be an additional risk factor for CVD (De Backer 1997; Fowkes et al. 1999). Indeed, the mean BMI of the index patients in our study was 26.8 (Table 4). Many studies considered BMI to be more important in females than in males (De Backer 1997; Fowkes et al. 1999). In our study, however, only a small yet significant difference ($P = 9.2 \times 10^{-7}$) difference was observed between the mean BMI of males (27.5, SD 3.7) and females (26.6, SD 5.0; Table 4). However, obesity

seems to play a more important role for the development of severe forms of CVD (26.5 for C3, via 28.3 for C4, to 29.6 for C5&C6; Table 5). Indeed, in a two-factor analysis of variance, sex and CEAP grade both had a significant effect upon BMI ($P = 7.8 \times 10^{-6}$ and $P = 2.2 \times 10^{-16}$).

Two major strengths of our study have been (1) the use of a high-risk population, thereby resulting in a higher prevalence of both simple VV and CVI than, for example, the Bonn Vein Study (Rabe et al. 2003), and (2) a large number of nuclear families available for heritability analysis. Unfortunately, all data other than those on index patients were self-reported. However, we do not regard this as a major source of upward bias for our heritability estimates because, if anything, a less than perfect patient recall will have introduced additional variance into the analysis, thereby leading to an underestimate of the true level of familiarity of CVD. Another possible drawback may have been that, by definition, h^2 is population-dependent, i.e. h^2 estimates from one population do not necessarily reflect the heritability of the same trait in another population (Visscher et al. 2008). Therefore, future studies are required to clarify whether our heritability estimate is indeed representative of CVD in general. These limitations notwithstanding, our results strongly encourage efforts to identify susceptibility genes predisposing for severe forms of CVD.

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