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ORIGINAL ARTICLE

Intrinsic biventricular dysfunction in Marfan syndrome

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ABSTRACT

Background Marfan syndrome (MFS) is an autosomal, dominantly inherited, connective tissue disorder usually caused by a mutation in the fibrillin-1 gene (*FBN1*). As fibrillin-1 is a component of the extracellular matrix of the myocardium, mutations in *FBN1* may cause impairment of ventricular function. Furthermore, aortic elasticity is decreased in patients with MFS, which might also impair ventricular function. We assessed biventricular function and the influence of aortic elasticity in patients with MFS by means of cardiac MRI.

Methods and results Cardiac magnetic resonance was performed in 144 patients with MFS without significant valvular dysfunction, previous cardiac surgery or previous aortic surgery. Biventricular diastolic and systolic volumes were measured, and ejection fractions were calculated. Flow wave velocity, a measurable derivative of aortic elasticity, was measured between the ascending aorta and the bifurcation. When compared to healthy controls ($n=19$), left ventricular ejection fraction (LVEF) was impaired in patients with MFS ($53\pm 7\%$ vs $57\pm 4\%$, $p<0.005$), as was right ventricular ejection fraction (RVEF) ($51\pm 7\%$ vs $56\pm 4\%$, $p<0.005$). LVEF and RVEF were strongly correlated ($r=0.7$, $p<0.001$). No significant differences were found between patients with β -blocker treatment and those without. There was no correlation between aortic elasticity as measured by flow wave velocity and LVEF.

Conclusions Biventricular ejection fraction was impaired in patients with MFS, and the impairment was independent of aortic elasticity and β -blocker usage. There was also a strong correlation between LVEF and RVEF. Our findings suggest intrinsic myocardial dysfunction in patients with MFS.

Clinical trial registration <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1423>. Unique Identifier: NTR1423

INTRODUCTION

Marfan syndrome (MFS) is an autosomal, dominantly inherited, connective tissue disorder with characteristic features primarily involving the ocular, skeletal and cardiovascular system.¹ MFS is diagnosed according to the Ghent nosology and is usually caused by a mutation in the gene encoding the extracellular matrix (ECM) protein fibrillin-1 (*FBN1*).² Besides serving as a structural component of the ECM, fibrillin-1 also binds and inactivates transforming growth factor- β (TGF- β).³ Mutations in *FBN1* lead to abnormal signalling of the TGF- β cytokine family, which controls cell differentiation and proliferation, resulting in the phenotypic

characteristics of MFS. The most important cardiovascular characteristic of MFS is aortic root dilatation, predisposing to aortic dissection and rupture, which are the leading causes of morbidity and mortality in patients with MFS. Due to improved diagnosis, β -blocker treatment and most importantly prophylactic aortic root replacement, survival has improved significantly in the last decades.⁴ Another common cardiovascular manifestation of MFS is mitral valve prolapse, which may cause severe mitral regurgitation requiring surgical intervention. Besides these well-established cardiovascular manifestations of MFS, there are clues suggesting a ventricular dysfunction in patients with MFS that is independent of the presence of valvular disease. Given the fact that fibrillin-1 is a component of the ECM of the myocardium and that it binds and inactivates TGF- β , it may be surmised that mutations in *FBN1* cause impairment of ventricular function. Furthermore, aortic wall elasticity is reduced in patients with MFS, which may augment left ventricular function through 'ventricular arterial coupling'.^{5–8} Indeed, the results of previous echocardiography studies and a small study using cardiac MRI suggested the presence of ventricular dysfunction in patients with MFS, although the data were conflicting and inconclusive.^{9–15} In addition, a recent, somewhat larger study assessing ventricular function using cardiac magnetic resonance (CMR) provided evidence for biventricular dysfunction in patients with MFS.¹⁶ However, the effect of aortic elasticity on ventricular function was not taken into account in any of these studies. Recently, a study on 26 patients with MFS found that decreased aortic elasticity, as measured by applanation tonometry, influenced left ventricular systolic function, as measured by mitral annular displacement.¹⁷ In the present study, we performed CMR to establish left ventricular and right ventricular function in a large cohort of 144 patients with MFS, and we related the findings on ventricular function to aortic elasticity. Left and right ventricular dimensions and function were compared with a group of healthy controls.

METHODS

Study subjects

All study subjects with MFS were participants of the Cozaar in Marfan Patients Reduces Aortic Enlargement (COMPARE) study.¹⁸ Briefly, the COMPARE study investigates the effect of losartan on aortic growth in patients with MFS. Inclusion criteria of the COMPARE study were diagnosis of

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MFS according to the Ghent criteria¹⁹ and age ≥ 18 years. Exclusion criteria were current pregnancy, ACE inhibitor or angiotensin receptor blocker usage, previous replacement of more than one part of the aorta and previous aortic dissection. In the present predefined substudy, we excluded patients with 'significant' (ie, more than mild) aortic or mitral valve regurgitation as well as patients with any previous cardiac or aortic surgery. Figure 1 shows a flow chart of how the patients were selected for the study. Control subjects were healthy volunteers recruited among colleagues of one of the researchers. None of them was known to have cardiovascular disease. The ethics committees of the participating centres gave approval, and patients gave written and oral informed consent.

Cardiac MRI

Aortic diameters, ventricular volumes and aortic elasticity were assessed in all patients by CMR at the time of inclusion in the COMPARE trial. This was performed with a 1.5-Tesla MR system (Sonata/Avanto, Siemens, Erlangen, Germany) using a phased array cardiac receiver coil. ECG-gated cine images were acquired during breath-hold using segmented, steady-state, free-precession sequence. Short-axis views were obtained every 10 mm, starting

from the base up to the apex and covering both entire ventricles. To visualise the entire aorta, a three-dimensional, T1-weighted, spoiled gradient-echo sequence was used after administration of intravenous gadolinium. A high-resolution, gradient-echo pulse sequence with a velocity encoding gradient was applied perpendicular to the aorta at the level of the ascending aorta and just above the bifurcation. This resulted in multiphase modulus and phase-coded images with a temporal resolution of 25 ms. Participants had a washout period of 3 days for β -blocker treatment prior to CMR, as β -blocker treatment influences aortic elasticity in patients with MFS by shifting the pressure-area relation of the aorta to the elastin-determined part.²⁰

Echocardiography

Routine echocardiography was performed in all patients in the COMPARE study to evaluate valvular dysfunction and aortic root dimensions. Severity of aortic and mitral valve regurgitation was defined according to the European Society of Cardiology guidelines on valvular heart disease of 2007.²¹ Significant aortic regurgitation was defined as a ratio >0.25 of the width of the regurgitant stream at the level of the aortic valve relative to the size of the left ventricular outflow tract measured in the parasternal long-axis view. Significant mitral regurgitation was defined as a regurgitant jet of more than 4 cm² or more than 20% of the left atrial area.

Image analysis

MASS and FLOW image analysis software (Medis, Leiden, the Netherlands) were used for analyses on a separate workstation by one experienced investigator (JJJA). The slices at the base of the heart were considered to be in the ventricle if the blood was at least half surrounded by ventricular myocardium.

Endocardial contours of the left and right ventricle were manually traced in end-systole and end-diastole on all short-axis images in each patient, where end-diastole was defined as the phase with the largest ventricular area and end-systole as the phase with the smallest ventricular area. Left and right ventricular end-diastolic and end-systolic volumes were determined, and the left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) were calculated. Epicardial contours of the left ventricle were manually traced in end-diastole on all short-axis images in each patient, allowing calculation of left ventricular mass.

Aortic contours were drawn manually on the modulus images of all cardiac phases, and flow (m/s) through both aortic levels was calculated using the areas on the modulus images and the velocity values of the corresponding velocity encoded images. Distances between the levels were measured on the console by drawing a line through the middle of the aortic lumen on the oblique sagittal images. Flow wave velocity (FWV), the propagation velocity of the flow wave through the aorta, was calculated as the ratio of the distance between these levels and the time difference between arrival of the flow wave at these levels. FWV from the entire aorta was calculated (ie, from ascending aorta to the bifurcation) and taken as a measure of overall aortic elasticity. Data on the reproducibility of this FWV measurement have been published previously by our group,⁶ and the measurement is validated in vivo.²³

Aortic diameters were measured at five levels: the aortic root, the ascending and descending thoracic aorta at the level of the pulmonary artery, at the level of the diaphragm and just above the bifurcation. The aortic root was measured in end-diastole from leading edge to leading edge. The other diameters were measured on the angiogram.

Figure 1 Flow chart of selecting patients from the Cozaar in Marfan Patients Reduces Aortic Enlargement (COMPARE) study for this ventricular function study.

Statistical analysis

Continuous variables are shown as mean $\pm$ SD and categorical variables as percentages. Continuous variables with a normal distribution were compared using the independent-samples *t* test. Mann–Whitney *U* test was used to compare non-normally distributed variables. Multivariate linear regression was used to determine the effect of demographic and clinical variables on LVEF. A *p* value <0.05 was considered significant. The statistical package SPSS V.18 was used for analysis.

RESULTS

Demographic and clinical characteristics

We studied 144 patients with MFS (70 men and 74 women) and 19 healthy volunteers (9 men and 10 women) (figure 1). In total, there were 226 patients with MFS included in the original COMPARE study, of which five had a contraindication for CMR and 72 were excluded from our study because they had undergone previous cardiac surgery (valvular surgery or aortic root surgery) or had significant aortic or mitral valve dysfunction. Of the remaining 149 patients, we could not assess the left ventricular function in five patients for one of the following reasons: triggering problems, poor image acquisition, claustrophobia or an adverse reaction to gadolinium during image acquisition. Demographic and clinical characteristics are shown in table 1. Patients with MFS were taller compared to controls (mean height 187 $\pm$ 11 cm vs 178 $\pm$ 9 cm, *p*<0.005), and the aortic root was relatively large (43.3 $\pm$ 4.9 mm), as expected in a population of patients with MFS. Ninety-seven patients used β -blocker treatment (67%); no other cardiovascular medication was used.

CMR

End-diastolic and end-systolic volumes of both ventricles, corrected for body surface area (BSA), are shown in table 2. End-diastolic volume of the left ventricle corrected for BSA was not significantly enlarged in patients with MFS when compared to the controls. End-systolic volume was significantly larger (40 $\pm$ 11 vs 34 $\pm$ 7 in the controls, *p*=0.008) and LVEF was impaired in patients with MFS (53% $\pm$ 7% vs 57% $\pm$ 4% in the controls, *p*<0.005). Thirteen patients with MFS had an LVEF <45% (table 3). None of these patients had a diagnosis or history of heart failure, as assessed by the attending physician. Three out of these 13 patients also had an enlarged left ventricular end-diastolic volume corrected for BSA, age and gender, thus fulfilling the diagnosis of dilated cardiomyopathy. End-systolic volume of the right ventricle was significantly larger in patients with MFS (41 $\pm$ 13 ml/m² vs 35 $\pm$ 7 ml/m², *p*=0.02), and RVEF was significantly impaired when compared to the controls (51% $\pm$ 7% vs 56% $\pm$ 4%, *p*<0.005).

The correlations between LVEF and RVEF and demographic and clinical variables are shown in table 4. LVEF was significantly related with age, body mass index and heart rate. After multivariable linear regression analysis, all three variables remained independent predictors for LVEF. There was no relation between LVEF and β -blocker use (mean LVEF 53% $\pm$ 1% for β -blocker use vs 52% $\pm$ 1% for no β -blocker, *p*=0.62). Similarly, LVEF was not related with aortic elasticity as measured by FWV. RVEF was significantly related with age, sex and height. Because of a high degree of multi-collinearity between these variables, we performed a backward multivariable regression analysis, demonstrating that RVEF was significantly related with male sex (β -0.253, *p*=0.004). No relation was found between FWV and left ventricular mass (*r*=0.01, *p*=0.90), but FWV was

Table 1 Demographic and clinical characteristics

	Marfan (n=144)	Control (n=19)	p Value
Age (years)	36 $\pm$ 12	34 $\pm$ 9	0.5
Male	70 (49)	9 (46)	1
Height (cm)	187 $\pm$ 11	178 $\pm$ 9	<0.005
Weight (kg)	78 $\pm$ 15	73 $\pm$ 18	0.2
BSA (m ²)	2.0 $\pm$ 0.2	1.8 $\pm$ 0.2	<0.005
BMI (kg/m ²)	22.5 $\pm$ 4.1	22.1 $\pm$ 1.8	0.6
Heart rate (bpm)	66.2 $\pm$ 12.7	70.3 $\pm$ 10.5	0.1
Systolic blood pressure (mm Hg)	124 $\pm$ 13		
Diastolic blood pressure (mm Hg)	74 $\pm$ 10		
Mean arterial pressure (mm Hg)	91 $\pm$ 10		
Mitral valve prolapse	37 (26)		
Mild mitral valve regurgitation	43 (30)		
Mild aortic valve regurgitation	11 (8)		
Left ventricular mass (g)	97 $\pm$ 25		
Aortic root (mm)	43.3 $\pm$ 4.9		
Aortic root/BSA (mm/m ²)	21.8 $\pm$ 3.0		
Ascending aorta (mm)	29.4 $\pm$ 4.1		
Ascending aorta/BSA (mm/m ²)	14.8 $\pm$ 2.4		
Aortic arch (mm)	23.5 $\pm$ 3.6		
Aortic arch/BSA (mm/m ²)	11.8 $\pm$ 2.0		
Descending aorta (mm)	23.2 $\pm$ 3.4		
Descending aorta/BSA (mm/m ²)	11.7 $\pm$ 1.8		
FWV (m/s)	5.5 $\pm$ 1.2		
β -Blocker treatment	97 (67)		

Values are expressed as mean $\pm$ SD or n (%).

BMI, body mass index; BSA, body surface area; FWV, flow wave velocity.

positively related with mean arterial pressure (*r*=0.24, *p*=0.01), and left ventricular mass was positively related with systolic blood pressure (*r*=0.2, *p*=0.04). Finally, we found that there was a significant correlation (*r*=0.7, *p*<0.005) between LVEF and RVEF (figure 2).

DISCUSSION

In the largest study evaluating ventricular function in patients with MFS by CMR thus far, we demonstrated a reduced LVEF in patients with MFS compared to healthy individuals. We found that the impairment of ventricular function was independent of aortic elasticity. In addition, RVEF was also reduced in patients with MFS, and there was a strong correlation between left and right ventricular function. Together, our findings strongly support the existence of a cardiomyopathy as an integral part of MFS, which can occasionally be more severe than merely mild.

Table 2 Ventricular dimensions and function

	Marfan	Control	p Value
Left ventricle			
End-diastolic volume/BSA (ml/m ²)	84 $\pm$ 18 (36–134)	80 $\pm$ 13 (56–110)	0.4
End-systolic volume/BSA (ml/m ²)	40 $\pm$ 11 (16–77)	34 $\pm$ 7 (20–43)	0.008
Ejection fraction (%)	53 $\pm$ 7 (38–70)	57 $\pm$ 4 (53–67)	<0.005
Right ventricle			
End-diastolic volume/BSA (ml/m ²)	83 $\pm$ 19 (30–140)	80 $\pm$ 13 (60–114)	0.3
End-systolic volume/BSA (ml/m ²)	41 $\pm$ 13 (16–89)	35 $\pm$ 7 (25–50)	0.02
Ejection fraction (%)	51 $\pm$ 7 (32–70)	56 $\pm$ 4 (46–62)	<0.005

BSA, body surface area.

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Table 3 Patients with a left ventricular ejection fraction <45%

	Sex (M/F)	Age (years)	Height (cm)	Weight (kg)	BSA (m ²)	LVEDV/BSA (ml/m ²)	LVESV/BSA (ml/m ²)	LVEF (%)	FWV (m/s)
1	M	36	201	95	2.3	82	51	38	5.2
2	F	18	185	67	1.9	86	53	38	5.2
3	M	18	194	67	1.9	106	65	39	4.5
4	M	22	197	84	2.1	89	54	40	4.1
5	M	31	210	80	2.1	107	64	40	5.4
6	M	35	192	80	2.1	87	52	41	5.2
7	M	49	186	85	2.1	58	34	42	5.9
8	M	33	205	74	2.1	133	77	42	4.9
9	F	44	181	86	2.1	86	50	42	4.7
10	F	32	169	43	1.4	60	35	43	4.8
11	M	26	204	71	2	113	65	43	5.8
12	M	21	202	75	2.1	117	66	44	5.1
13	M	32	201	117	2.6	65	37	44	5.3

M, male; F, female; BSA, body surface area; FWV, flow wave velocity; LVEDV, end-diastolic volume of the left ventricle; LVESV, end-systolic volume of the left ventricle; LVEF, left ventricle ejection fraction.

Note: Patients 8, 11 and 12 had an enlarged end-diastolic volume of the left ventricle corrected for BSA, age and gender. Patient 1 developed an episode of heart failure after aortic root replacement (David procedure) 6 months after the inclusion in this study, requiring a prolonged intensive care unit admission. None of the other patients included in our study developed an episode of heart failure.

Previous studies

The first studies evaluating ventricular function in MFS used conventional echocardiography and did not find impairment in left ventricular systolic function.^{9 10 13 15 24} With evolving echocardiographic techniques, mild systolic and diastolic dysfunction was found in multiple studies.^{11 14 25} Most echo-

cardiographic studies, however, did not find a reduction in ejection fraction, which is the most widely used measure of systolic function.

Alpendurada *et al* retrospectively assessed ventricular function by CMR in 68 patients with MFS.¹⁵ They found a mean LVEF of 62% and a reduced ejection fraction in 25% of the patients. In our study, we found a lower mean LVEF in patients with MFS (53%±7%) and controls (57%±4%). Age in both studies was comparable (34±12 years vs 36±12 years in our study), as was aortic root diameter (44.6±6 mm vs 43.3±5 mm in our study). β-Blocker usage was higher in our study (67% vs 54%), but this did not affect ventricular function results in either study.

In addition, De Backer *et al* found a significantly reduced LVEF in patients with MFS compared to age- and sex-matched controls in a smaller study using CMR (54% vs 60%).¹¹ An older study evaluating ventricular function in children with MFS by CMR found no difference in LVEF between patients with MFS and healthy controls.¹⁵ This might be explained by the relatively small patient population studied in combination with a less accurate CMR technique.

Table 4 Correlations of LVEF and RVEF with demographic and clinical variables in patients with MFS

	LVEF		RVEF	
	β	p Value	β	p Value
Age	0.3	<0.005	0.22	0.01
Sex	-0.05	0.6	0.26	<0.005
Height	-0.16	0.1	-0.28	<0.005
Weight	0.13	0.1	-0.08	0.36
BSA	0.06	0.5	-0.15	0.08
BMI	0.23	0.006	0.10	0.24
Heart rate	-0.2	0.04	-0.09	0.32
β-Blocker usage	0.04	0.6	0.02	0.8
Systolic blood pressure	0.05	0.6		
Diastolic blood pressure	-0.12	0.2		
Mean arterial pressure	-0.05	0.5		
Mitral valve prolapse	-0.11	0.2		
Mild mitral valve regurgitation	-0.01	0.9		
Mild aortic valve regurgitation	0.07	0.4		
Left ventricular mass	-0.13	0.14		
Aortic root diameter	-0.07	0.4		
Aortic root/BSA	-0.15	0.09		
Ascending aorta diameter	0.13	0.1		
Ascending aorta diameter/BSA	0.03	0.8		
Aortic arch diameter	-0.01	0.9		
Aortic arch diameter/BSA	-0.66	0.4		
Descending thoracic aorta diameter	0.09	0.3		
Descending thoracic aorta diameter/BSA	-0.01	0.9		
FWV	0.12	0.2		

BSA, body surface area; BMI, body mass index; FWV, flow wave velocity; LVEF, left ventricular ejection fraction; MFS, Marfan syndrome; RVEF, right ventricular ejection fraction.

Role of aortic elasticity and other factors

In MFS, aortic elasticity (of which FWV is a measurable derivative) is decreased compared to healthy individuals.^{6 26–28} This reduction in aortic elasticity in patients with MFS might influence ventricular function because of increased afterload, through ventricular–arterial coupling. Mean FWV was 5.3 m/s in our study. FWV was in the same order of magnitude as in our previous studies investigating aortic elasticity in patients with MFS by means of CMR.^{6 29 30} In these studies, FWV was significantly higher in patients with MFS compared to a matched control group (5.2 m/s vs 4.3 m/s, $p<0.001$), suggesting that aortic elasticity was also reduced in the present patient group. However, we found no significant relation between LVEF and FWV, suggesting that the impairment of ventricular function was not due to reduced aortic elasticity. Neither did we find a significant relation between FWV and left ventricular mass, which supports this finding. Only one study had previously evaluated the relationship between aortic elasticity and ventricular function in MFS:¹⁷ they evaluated pulse wave velocity, measured by applanation tonometry, and left ventricular function, measured by mitral annular displacement, on echocardiography in 26 patients with MFS and compared these with 30 normal controls. They found that increased carotid–femoral pulse wave velocity was associated with

Figure 2 Relation between left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF).

reduced left ventricular longitudinal systolic function. They did not, however, find a significant relation between carotid–radial pulse wave velocity and left ventricular longitudinal systolic function. Unfortunately, they gave no explanation for this finding. They also found a reduced LVEF measured by echocardiography (66% vs 70%), but did not perform a regression analysis with the ejection fraction as a dependent variable. It is therefore difficult to compare their findings with our study.

We found that age was positively related with LVEF (albeit rather weak), while LVEF is known to remain relatively stable during life in healthy individuals.³¹ This unexpected finding can possibly be explained by the exclusion of patients with aortic dissection, operated patients and patients with significant valvular dysfunction. As a consequence, the older patients included in our study were probably relatively mildly affected by MFS, which might also apply to ventricular function. Male sex was associated with lower RVEF, which is in line with the reference values provided by multiple studies.^{22 32 33} Finally, we found a strong correlation between LVEF and RVEF ($r=0.7$, $p<0.05$). Together, these findings support the existence of a cardiomyopathy affecting both ventricles as an integral part of MFS, which is usually merely mild but can also be more severe. Our finding of a dilated cardiomyopathy in three patients with MFS without significant valvular regurgitation or previous cardiac surgery supports this conclusion.

Pathophysiology

Fibrillin-1, the major constituent of microfibrils, is present in the myocardium as an integral part of the normal myocardial ECM, and it is particularly found at sites where myocardial contraction transmits power to the ECM.^{34 35} Although the present study was not designed to address the underlying pathophysiology, it is conceivable that deficient fibrillin-1 causes impairment of myocardial contraction. Furthermore, deficient fibrillin-1 leads to an altered TGF- β expression in the ECM of the myocardium.³ Excess TGF- β in the ECM of the myocardium possibly leads to altered genetic expression through activation of the SMAD pathway and, consequently, to myocardial structural changes. TGF- β is also known to be involved in fibrosis in pressure-loaded heart failure³⁶ and to be overexpressed in the myocardium of patients with idiopathic hypertrophic cardiomyopathy.³⁷ Losartan, an ATII blocker with TGF- β antagonising properties, has the potential to improve the myocardial function in MFS. At the moment, there are several trials evaluating the effects of losartan on aortic growth and ventricular function in patients with MFS.^{18 38–40}

Key messages

An intrinsic myocardial dysfunction is present in patients with MFS.

Study limitations

First, we did not analyse the diastolic ventricular function, although it would be interesting to evaluate whether the decrease in aortic elasticity is related to diastolic dysfunction secondary to ventricular–arterial coupling. Second, since our control group was not a case control group, it could not be used as a reference population. With 19 patients in the control group, however, we had enough power ($>95\%$) to detect a significant difference in ventricular function.

Possible clinical implications

Overt heart failure in the absence of significant valvular regurgitation is rare in patients with MFS. However, since significant impairment of ventricular function may occur, it seems reasonable to perform at least one CMR with assessment of ventricular function in all patients with MFS. If an impaired ejection fraction is found, tailored treatment with an ACE inhibitor or angiotensin receptor blocker should be considered to prevent further deterioration of ventricular function or peri-operative episodes of heart failure, especially in patients who also have an enlarged end-diastolic volume of the left ventricle.

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Competing interests None.

Ethics approval Ethics approval was provided by Medical Ethics Committee, Academic Medical Center Amsterdam, the Netherlands.

Contributors Piet de Witte: conception and design of study; collection, analysis and interpretation of data; writing of the manuscript. Jan J.J. Aalberts: analysis of data, critically commenting and amending the manuscript. Teodora Radonic: conception and design of study, collection of data, critically commenting and amending the manuscript. Janneke Timmermans: collection of data, critically commenting and amending the manuscript. Arthur J. Scholte: collection of data, critically commenting and amending the manuscript. Aeilko H. Zwinderman: conception and design of study, analysis and interpretation of data, critically commenting and amending the manuscript. Barbara J.M. Mulder: conception and design of study, collection of data, critically commenting and amending the manuscript. Maarten Groenink: conception and design of study, collection of data, critically commenting and amending the manuscript. Maarten P. van den Berg: conception and design of study, analysis and interpretation of data, critically commenting and amending the manuscript.

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