Thr164Ile polymorphism of ß2-adrenergic receptor negatively modulates cardiac contractility: implications for prognosis in patients with idiopathic dilated cardiomyopathy

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MOLECULAR BIOLOGY AND GENETICS

Thr164*Ile* polymorphism of β2-adrenergic receptor negatively modulates cardiac contractility: implications for prognosis in patients with idiopathic dilated cardiomyopathy

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Background: β2-adrenergic receptor Thr164*Ile* (threonine (Thr) is replaced by an isoleucine (*Ile*) at codon 164) polymorphism was postulated to contribute to lower exercise tolerance and poor prognosis in patients with congestive heart failure. However, heart failure is associated with several abnormalities of β receptor signalling, and underlying mechanisms are not clear.
Objectives: To investigate whether Thr164*Ile* polymorphism negatively modulates myocardial contractile performance and is associated with adverse long-term prognosis of patients with congestive heart failure.
Methods: Among 55 subjects, cardiac contractile response to the β2-adrenergic receptor agonist terbutaline was assessed from the peak myocardial velocity of systolic shortening (Sm) in 18 subjects with the *Ile*-164 variant and 37 matched controls. In total, 24 subjects had normal left ventricular (LV) function and 31 presented with congestive heart failure due to idiopathic dilated cardiomyopathy.
Results: In patients with normal LV function, peak terbutaline-induced increase (Δ) in Sm was lower in subjects with the *Ile*-164 variant than in controls (Δ33% (4%) vs Δ56% (4%), $p<0.01$). In patients with heart failure, subjects with *Ile*-164 showed further severe reduction of β2-adrenergic-mediated increase in Sm as compared with controls with heart failure (Δ20% (5%) vs Δ39% (4%), $p<0.05$). Patients with heart failure with *Ile*-164 showed a severely blunted force–frequency relationship in response to agonist stimulation. At 2-years of follow-up, patients with heart failure with the *Ile*-164 variant showed higher incidence of adverse events than controls with heart failure (75% (6/8)] vs 30% (7/23), $p<0.05$).
Conclusions: The β2-adrenergic Thr164*Ile* polymorphism directly modulates adrenergic-mediated cardiac responses in patients with normal and failing myocardium. Furthermore, blunted β2 adrenergic-mediated myocardial contractile response in patients with *Ile*-164 variant seems to adversely modulate the course of congestive heart failure.

In the normal myocardium, β2-adrenergic receptors represent ~20% of the total β-adrenergic receptor population, and, similar to β1-adrenergic receptors, they mediate cardiac inotropic and chronotropic responses.[1] In congestive heart failure, chronic activation of the cardiac sympathetic nervous system leads to abnormalities at several levels of the adrenergic receptor signal transduction pathway. A reduction in the number of receptors (down regulation) and responsiveness (uncoupling) cause blunted adrenergic-mediated responses that contribute to the progression of congestive heart failure.[1] β2-adrenergic receptor desensitisation is mainly determined by the uncoupling phenomenon.[2] The number of receptors remains relatively stable and this is considered to be one of the compensatory mechanisms preserving adrenergically mediated cardiac responses in heart failure.[3 4]

The β2-adrenergic receptor gene polymorphism, in which a threonine (Thr) is replaced by an isoleucine (*Ile*) at codon 164 (Thr164*Ile*), leads to ''loss of the function'' of the receptor.[5] Despite the rare incidence,[6] individuals with the *Ile*-164 allele and normal left ventricular (LV) function show blunted haemodynamic responses to adrenergic stimulation.[7] Furthermore, patients with heart failure with Thr164*Ile* polymorphism seem to be characterised by reduced exercise tolerance and higher mortality.[6 8] However, pathophysiological mechanisms contributing to the poor outcome of these patients are not clear—namely, it is unclear whether the poor outcome is related to direct effects of the *Ile*-164 polymorphism on the myocardial contractile performance or to systemic haemodynamics. Earlier studies[1 3] indicated that β2-adrenergic receptors may be also hyporesponsive (uncoupled) in heart failure, which is raising doubts about the importance of the Thr164*Ile* polymorphism in the modulation of myocardial contractility in patients with failing myocardium. Accordingly, we investigated β2-agonist-mediated contractile performance in patients with normal and failing myocardium to test the hypothesis that the dysfunctional *Ile*-164 β2-adrenergic receptor directly modulates myocardial contractile performance. Second, we studied the effect of the *Ile*-164 variant on long-term prognosis of patients with congestive heart failure due to idiopathic cardiomyopathy.

METHODS

Study population

A total of 786 Caucasian patients referred to cardiac catheterisation because of chest pain or dyspnoea were screened for β2-adrenergic receptor polymorphisms in codons 16, 27 and 164. An additional 100 healthy Caucasian blood donors were screened and served as control population. Among screened patients, 55 were eligible for further functional studies. Exclusion criteria were LV hypertrophy, hypertension, valvular heart diseases or coronary artery stenosis with >30%. Informed consent was obtained from all subjects. The study was approved

Abbreviations: LV, left ventricular; LVEF, left ventricular ejection fraction; Sm, peak myocardial velocity of systolic shortening; Thr164*Ile*, threonine (Thr) is replaced by an isoleucine (*Ile*) at codon 164

by the ethical committee of the OLV Ziekenhuis, Aalst, Belgium.

DNA genotyping

Genomic DNA was subjected to a PCR. To amplify the polymorphic site (nucleotide 491), the following primers were used: 5′-CTT-TTG-GCA-ACT-TCT-GGT-GCG-AG-3′ (forward) and 5′-AGT-CAC-AGC-AGG-TCT-CAT-TG-3′ (reverse; TIB MOLBIOL, Berlin, Germany). The amplification was performed on the LightCycler (Roche Molecular Biochemicals, Mannheim, Germany) using the following hybridisation probes: 5′-TTG-TGT-CAG-GCC-TTA-CCT-CCT-TCT-T-3′ (donor dye, labelled with fluorescein) and 5′-LCRed640-CCC-ATT-CAG-ATG-CAC-TGG-TAC-AGG-GC-3′ (acceptor dye, labelled with LightCycler-Red640). The reaction conditions consisted of 10 ng DNA, 300 μM of each deoxyribonucleotide triphosphate, 3.25 mM $MgCl_2$, 5% bovine serum albumin, 0.5 μM of each primer, 0.2 μM of each probe, 0.05 U/μl Taq-polymerase and a ×10 dilution of the supplied buffer in a final volume of 10 μl. PCR conditions were initial denaturation of 95℃ for 5 min, then 40 cycles of 95℃ for 15 s, 59℃ for 5 s and 72℃ for 10 s, followed by melting from 95℃ for 10 s to 40℃ for 20 s and an increase to 85℃ with a speed of 0.2℃/s and a final cooling to 40℃. Genotype frequencies in our control population were as follows: Arg16Arg 44%, Arg16Gly 21%, Gly16Gly 35%; Gln27Gln 32%, Gln27Glu 53%, Glu27Glu 15%; and Thr164Thr 98%, Thr164*Ile* 2%. In patients with low LV ejection fraction (LVEF <45%), genotype frequencies were not statistically different from control population: Arg16Arg 47%, Arg16Gly 15%, Gly16Gly 38%; Gln27Gln 37%, Gln27Glu 47%, Glu27Glu 16%; and Thr164Thr 95%, Thr164*Ile* 5%.

Tissue Doppler ECG

Pulsed-wave Doppler recordings of longitudinal myocardial velocities of basal segments were obtained in standard apical views as described previously, [9] using a commercial ultrasound system (Acuson Sequoia, Mountain View, California, USA). During the recording, a sample volume of 5 mm was positioned in the centre of the segment parallel to the long axis and 3–5 consecutive beats were averaged for the analysis.

Functional study protocol

Patients with LVEF <45% (as assessed by angiography) and LV end-diastolic diameter >60 mm were considered to have congestive cardiomyopathy. None of these patients had documented coronary artery disease. β Blockers, when present, were stopped 24–36 h before terbutaline protocol. Study population was divided according to genotype and LV function as follows: group 1: controls homozygotic for the Thr164Thr polymorphism, with normal LV function (n = 14); group 2: subjects heterozygotic for the Thr164*Ile* polymorphism, with normal LV function (n = 10); group 3: controls homozygotic for the Thr164Thr polymorphism, with congestive cardiomyopathy (n = 23); and group 4: subjects heterozygotic for the Thr164*Ile* polymorphism, with congestive cardiomyopathy (n = 8).

Haemodynamic and myocardial contractile performance was studied during the infusion of the selective β2-adrenergic receptor agonist terbutaline (Bricanyl, Pharmastern, Wedel, Germany). After a 1 h period of supine rest, intravenous terbutaline was increasingly infused at 25, 50, 100 and 150 ng/kg/min, each dose for 15 min.[7] Heart rate and blood pressure were continuously monitored throughout the study period.

Data analysis

At tissue Doppler imaging, myocardial contractile response was assessed from the peak myocardial velocity of systolic shortening (Sm) during ejection. This index has been recently introduced as an index of myocardial contractility and correlated well with invasive parameters.[10–13] Tissue Doppler analysis of Sm was performed by an experienced operator blinded to the clinical data and genotype of all subjects. Sm was averaged from four basal segments of the left ventricle (anterior, inferior, lateral and septal) at baseline and 30 s before the end of each dose of terbutaline.

Arterial pulse pressure, calculated as a difference between systolic blood pressure and diastolic blood pressure, was used as a surrogate for cardiac output.[14] All haemodynamic data were analysed by the observers blinded to the results of genotyping.

The population of patients with heart failure (groups 3 and 4) were followed from the date of entry into the study up to 2 years. Clinical end points were death, heart transplantation, worsening of heart failure requiring increase in diuretics or hospital admission and new onset of atrial fibrillation.

Statistical analysis

Data are expressed as mean (SEM). Two-sided Student's t test, Fisher's exact test and one-way analysis of variance followed by Newman Keuls post hoc analysis were used for appropriate comparisons. p Value <0.05 was considered significant. In patients with congestive heart failure, event-free survival at 2 years was calculated from the Kaplan–Meier estimates using the log rank test for comparison between patients with and without *Ile*-polymorphisms.

RESULTS

Clinical data

Table 1 shows the clinical characteristics of the patients. Groups were matched by age and LVEF. Female gender was slightly more frequent in patients with homozygotic Thr164Thr. No differences were found in the incidence of diabetes, renal failure and atrial fibrillation. There were no differences in medical treatment between patients with the *Ile*-164 variant and their respective control group, regarding the treatment with β blockers, ACE inhibitors or spironolactone.

Table 1 Baseline clinical characteristics of subjects with normal left ventricular function (groups 1 and 2) and patients with heart failure (groups 3 and 4)

	Group 1 (Thr/normal) n = 14	Group 2 (*Ile*/normal) n = 10	Group 3 (Thr/low LVEF) n = 23)	Group 4 (*Ile*/low LVEF) n = 8
Age (years)	60 (5)	61 (5)	64 (3)	62 (3)
Men/women	8/6	8/2	16/7	7/1
Diabetes	2/14	1/10	4/23	1/8
Renal failure	0/14	0/10	0/23	0/8
Atrial fibrillation	0/14	0/10	2/23	1/8
HR (bpm)	61 (2)	63 (2)	73 (3)*	70 (3)*
SBP (mm Hg)	124 (5)	133 (5)	110 (4)	114 (7)
DBP (mm Hg)	74 (2)	80 (2)	68 (3)	71 (3)
LVEF (%)	76 (3)	75 (2)	30 (3)*	33 (4)*
β blockers	4/14	4/10	16/23	8/8
ACE/AT1 blockers	3/14	3/10	20/23	8/8
Spironolactone	3/14	1/10	20/23	7/8
Diuretics	3/14	0/10	18/23	8/8

AT1, angiotensin II type 1; DBP, diastolic blood pressure; HR, heart rate; *Ile*, heterozygotic for Thr164*Ile*; low LVEF, patients with reduced left ventricular function; LVEF, left ventricular ejection fraction; normal, subjects with normal left ventricular function; SBP, systolic blood pressure; Thr, homozygotic for Thr164Thr.
Values are mean (SEM).
*p<0.01 versus groups 1 and 2.

Haemodynamics

Tables 1 and 2 show haemodynamic data. At baseline, patients with LV dysfunction had higher heart rate than individuals with normal LV function regardless of the genotype. In the subgroup of patients with LV dysfunction, no significant change in heart rate was observed during terbutaline in patients with the Thr164*Ile* polymorphism. At baseline, systolic and diastolic blood pressures were similar in all groups and did not change in response to terbutaline. No significant changes in LV end-diastolic dimensions during terbutaline were observed in all patients (data not shown).

Myocardial contractile response to terbutaline

Figure 1A shows dose-dependent changes of Sm in response to terbutaline in controls (Thr164Thr) and subjects (Thr164*Ile*) with normal LV function. Terbutaline induced a significant dose-dependent increase in Sm in subjects with Thr164*Ile* polymorphism. However, the increase in Sm was lower than in the matched controls without the polymorphism.

In patients with dilated cardiomyopathy (fig 1 B), controls with the wild-type Thr164Thr genotype showed a significant dose-dependent increase in Sm. Yet, as expected, the maximal increase was lower than in controls with the same wild-type genotype but normal LV function (table 2). Furthermore, patients with dilated cardiomyopathy and the *Ile*-164 variant showed only a minimal increase in Sm response to terbutaline, which was markedly lower than in patients with idiopathic cardiomyopathy and the Thr164Thr genotype.

Arterial pulse pressure

To further corroborate the myocardial contractile response assessed by the Sm, arterial pulse pressure was measured as an index of cardiac output.[14] At baseline, pulse pressure tended to be lower in both groups of patients (groups 3 and 4) with LV dysfunction (table 2). In individuals with normal LV function, pulse pressure increased in response to terbutaline in controls, whereas no changes were observed in carriers of the *Ile* variant. In patients with dilated cardiomyopathy, pulse pressure did not change in response to terbutaline in controls or in carriers of the *Ile* variant.

Force–frequency relationship

To investigate whether observed effects on the cardiac performance are directly related to effects of *Ile*-164 variant on the myocardial contractility, we analysed the force–frequency relationship at baseline and during peak terbutaline infusion (fig 2). In subjects with normal LV function, carriers of the *Ile*-164 variant showed a blunted increase in the force–frequency relationship at peak terbutaline infusion as compared with individuals without the *Ile*-164 variant. Notably, the slope of force–frequency relationship at baseline and at peak terbutaline remained similar, suggesting reduced chronotropic response as the main mechanism underlying blunted increase in contractility in these subjects. As expected, in patients with dilated cardiomyopathy with the Thr164Thr genotype, the force–frequency relationship at baseline and at peak terbutaline showed downward and rightward shift as compared with controls with normal LV function. Patients with the *Ile*-164 variant showed a further reduction in the slope of the force–frequency relationship as compared with controls with dilated cardiomyopathy and with carriers of the *Ile*-164 with normal LV function. This is consistent with blunted inotropic and chronotropic responses as underlying mechanisms of blunted myocardial performance to terbutaline in patients with the *Ile*-164 variant and idiopathic cardiomyopathy.

Clinical follow-up

Only one patient with the Thr164Thr genotype underwent heart transplantation and died 1 month after the surgery. No patient with the *Ile*-164 variant died or underwent heart transplantation. New York Heart Association class (2.2 (0.3) vs 1.35 (0.2), $p<0.05$), number of patients with worsening heart failure (50% vs 4%, $p<0.05$) or >1 event (50% vs 4%, $p<0.05$) was higher in patients with the *Ile*-164 variant than in patients with the Thr164Thr genotype. As fig 3 shows , the event-free period was significantly better in patients with heart failure with the wild-type receptor than in patients with the *Ile*-164 variant. In addition, at the 2-year follow-up, patients with heart failure with the Thr164Thr genotype showed a significantly higher increase in LVEF whereas no changes were noted in patients with heart failure with the *Ile*-164 variant (7.0% (2.3%) vs 0.1% (1.8%), $p<0.05$).

Table 2 Haemodynamic data and left ventricular performance at baseline and peak terbutaline

	HR (bpm)	SBP (mm Hg)	DBP (mm Hg)	Sm (cm/s)	PP (mm Hg)
Group 1 (Thr/normal)					
BL	61 (2)	124 (5)	74 (2)	9.7 (0.3)	50 (4)
Peak terb	83 (3)*	131 (5)	71 (3)	14.9 (0.5)*	59 (4)*
Group 2 (*Ile*/normal)					
BL	63 (2)	133 (5)	80 (2)	9.8 (0.3)	53 (4)
Peak terb	75 (3)*†	128 (6)	74 (3)	12.8 (0.4)*†	54 (6)
Group 3 (Thr/low LVEF)					
BL	73 (3)‡	110 (4)	68 (3)	8.5 (0.3)	44 (3)
Peak terb	82 (3)*	112 (4)	69 (3)	11.8 (0.5)*†	45 (3)
Group 4 (*Ile*/low LVEF)					
BL	70 (3)‡	114 (7)	71 (3)	8.9 (0.4)	43 (6)
Peak terb	78 (5)	112 (4)	67 (2)	10.5 (0.4)*§	45 (3)

BL, baseline; DBP, diastolic blood pressure; HR, heart rate; *Ile*, heterozygotic for Thr164*Ile*; low LVEF, patients with reduced left ventricular function; LVEF, left ventricular ejection fraction; normal, subjects with normal left ventricular function; PP, pulse pressure; SBP, systolic blood pressure; Sm, peak myocardial velocity of the systolic shortening; terb, terbutaline; Thr, homozygotic for Thr164Thr.
*$p<0.05$ versus corresponding values at BL.
†$p<0.05$ versus group 1 at peak terb.
‡$p<0.05$ versus groups 1 and 2 (at BL).
§$p<0.05$ versus group 3 at peak terb.

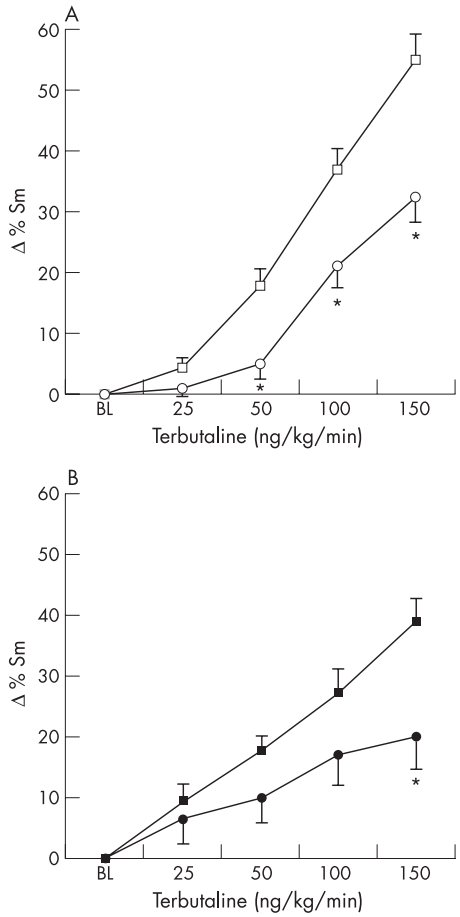

Figure 1 (A) Dose-dependent increase in peak myocardial velocity of the systolic shortening (Sm) in patients with normal left ventricular (LV) function. Open squares indicate controls with the Thr164Thr polymorphism. Open circles indicate subjects with the Thr164*Ile* polymorphism. *$p<0.05$ versus controls with the Thr164Thr. Comparison to preceding dose with $p<0.05$ (not shown in the figure) for controls with the Thr164Thr polymorphism at all terbutaline doses; for subjects with the Thr164*Ile* polymorphism at terbutaline doses of 50, 100 and 150 ng/kg/min. (B) Dose-dependent increase in Sm in patients with LV dysfunction. Full squares indicate controls with the Thr164Thr polymorphism. Full circles indicate patients with the Thr164*Ile* polymorphism. *$p<0.05$ versus respective controls. Comparison to preceding dose with $p<0.05$ (not shown in the figure) for controls with the Thr164Thr at all terbutaline doses; for patients with Thr164*Ile* at terbutaline doses of 50, 100 and 150 ng/kg/min. BL, baseline.

DISCUSSION

The present study investigates the effect of the Thr164*Ile* polymorphism of the β2-adrenergic receptors on cardiac contractility in normal subjects and in patients with LV dysfunction. Our data demonstrate that (1) subjects with Thr164*Ile* polymorphism and normal LV function show blunted chronotropic and contractile response to β2-adrenergic stimulation; (2) the Thr164*Ile* genetic variant is associated with absence of β2-adrenergically mediated myocardial contractile reserve in patients with idiopathic dilated cardiomyopathy; and (3) depressed contractile reserve in patients with heart failure with the Thr164*Ile* variant was associated with worse event-free survival than in controls with heart failure.

β-Adrenergic receptors in the normal and failing heart

The β-adrenergic receptors are the main regulators of cardiac inotropy and chronotropy.[1] Despite many similarities, β1-adrenergic and β2-adrenergic receptors have distinct genetic and pharmacological characteristics.[15] β1-Adrenergic receptors stimulate c-AMP production by interacting exclusively with G stimulatory proteins, whereas β2-aderenergic receptors can couple with both stimulatory and inhibitory G proteins. Furthermore, β1-adrenergic receptor-mediated responses are mainly related to c-AMP production, whereas β2-adrenergic receptor-mediated signalling is more complex and not entirely defined.[16–18]

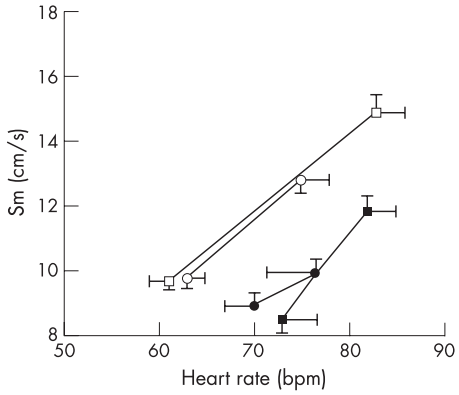

Figure 2 Force–frequency relationship at baseline and at peak terbutaline infusion. Sm, peak myocardial velocity of the systolic shortening.

Previous studies demonstrated that congestive heart failure is associated with several abnormalities of downstream signalling of β-adrenergic receptors.[3 19–22] In particular, dysfunctional myocardium is characterised by a down regulation of β1-adrenergic receptors, whereas the number of β2-adrenergic receptors remains relatively stable. In addition, in various experimental models, genetic manipulations of β2-adrenergic receptor-dependent signalling were shown to protect or even rescue LV function of the failing heart.[23–25] This corroborates the hypothesis that β2-adrenergic receptors play a pivotal role in the control of myocardial contractility of the failing heart. Accordingly, it was also hypothesised that genetic changes in receptor function could profoundly affect the course of heart failure. Nevertheless, β2-adrenergic receptors have been to be reported hyporesponsive in the failing myocardium,[1–4] questioning the significance of genetic variants in β2-adrenergic receptors in congestive heart failure.

Thr164*Ile* polymorphism and inotropic reserve in congestive heart failure

Genetic heterogeneity of the β2-adrenergic receptor with the replacement of threonine by isoleucine at codon 164 is associated with ''loss of function'' of the polymorphic receptor due to increased uncoupling.[5] The presence of this genetic variant caused blunted cardiac inotropic and chronotropic responses,[26] as well as impaired vasomotion.[27 28] In humans with normal LV function and Thr164*Ile* polymorphism, Brodde *et al*[7] reported a blunted increase in the duration of ECG-derived electromechanical systole, an indirect index of cardiac performance, in response to β2-adrenergic agonist stimulation.[29] Our findings of reduced myocardial contractile response and pulse pressure in similar subjects extend this observation and corroborate the postulate that the Thr164*Ile* polymorphism directly modulates the β2-adrenergic-mediated inotropic reserve. In addition, analysis of the force–frequency relationship suggests that the blunted contractile response in the carriers with normal function is mainly related to reduce chronotropic response.

However, in light of existing abnormalities in β2-adrenergic receptor signalling, it remains controversial whether similar

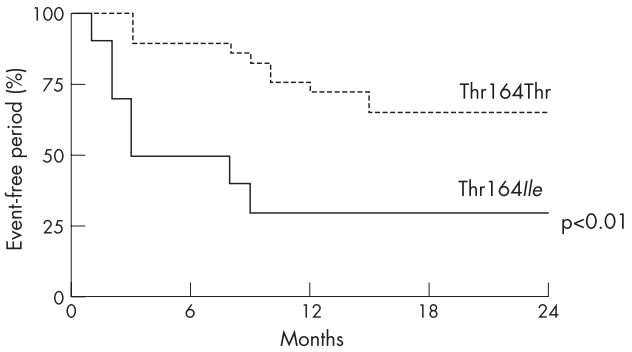

Figure 3 Event-free period in patients with heart failure with the Thr164Thr genotype (broken line) and the *Ile*-164 variant (continuous line).

effects would be observed in humans with failing myocardium. As expected, patients with dilated cardiomyopathy showed reduced myocardial contractile reserve and no change in arterial pulse pressure in response to terbutaline. Nevertheless, the *Ile*-variant was associated with further deterioration of contractile response and force–frequency relationship at peak terbutaline infusion. Unlike *Ile*-164 carriers with normal LV function, blunted increase in the force–frequency relationship in patients with idiopathic cardiomyopathy was related to reduction of both chronotropic and inotropic responses. Taken together, these observations suggest that the *Ile*-164 variant further attenuates β2-adrenergic receptor-mediated myocardial contractile response also in patients with failing myocardium.

Prognostic importance of Thr164*Ile* polymorphism in congestive heart failure

Only a few studies have addressed the clinical importance of the *Ile*-164 variant in heart failure in humans.[6 8] They suggested that patients with heart failure with the Thr164*Ile* polymorphism have lower exercise capacity[8] and may have higher mortality or progression to transplantation.[6] In our study, we failed to observe higher mortality or higher incidence of heart transplantation. However, it should be noted that our patients were characterised by higher LVEF and the vast majority of patients were treated with β blockers, which may account for the more favourable prognosis of our patient cohort. Nevertheless, the presence of the *Ile*-164 variant was associated with higher incidence of clinical events including worsening of heart failure. Thus, these data corroborate the hypothesis that the *Ile*-164 polymorphism is associated with attenuated contractile response to β2-adrenergic-mediated stimulation that may contribute to the worse clinical outcome in patients with heart failure.

Study limitations

The present study was not powered to investigate the effect of other alleles or haplotype combinations on β2-adrenergic responses. It should be acknowledged that polymorphisms at codons 16 and 27 may have influenced the observed differences in contractile response to terbutaline.[8] The incidence of both polymorphisms was similar between patients with dilated cardiomyopathy with and without the *Ile*-164 variant. By contrast, the incidence of both variants was lower in subjects with the Thr164*Ile* variant and normal LV function than in controls. Nevertheless, these subjects showed reduced contractile and haemodynamic response corroborating the notion that the *Ile*-164 variant is the main variant responsible for the blunted β2-adrenergic responsiveness. This study also has an intrinsic limitation in the number of selected patients owing to the rarity of the *Ile*-164 variant and the strict inclusion criteria used. The latter were necessary to ensure the absence of confounding factors, such as cardiac hypertrophy, ischaemic or valvular heart disease that could affect evaluation of cardiac contractile reserve.

Clinical implications

The present data demonstrate that the presence of the *Ile*-164 variant directly modulates β2-adrenergic-mediated myocardial contractile response in normal and in the failing human myocardium. Furthermore, the lower event-free period in patients with heart failure with this variant suggests that the presence of *Ile*-164 may also modulate progression and outcome in patients with congestive heart failure.

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Competing interests: None.

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IMAGES IN CARDIOLOGY

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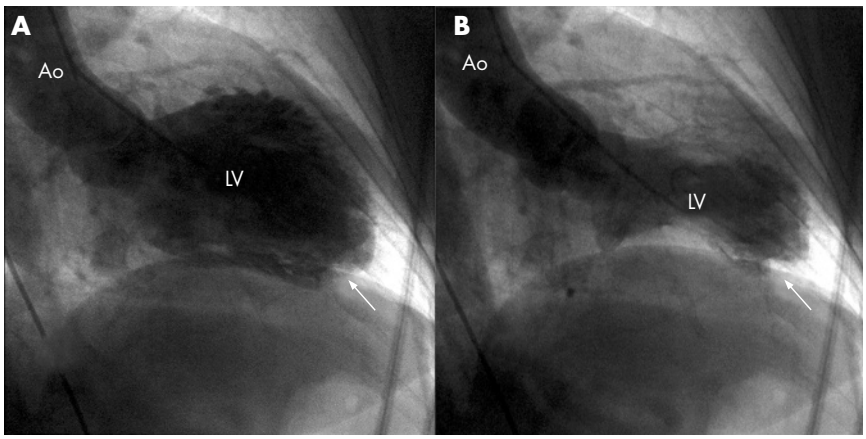
Left ventricular thrombus associated with left ventricular apical ballooning

A 74-year-old woman who had been experiencing mental stress was admitted to our institution with a history of continuous atypical chest pain. The evolutive ECG showed T wave inversion in leads V2–V6, I AVL and III, with a prolonged QT interval. Mild enzymatic changes were found in blood chemistry examinations. Coronary angiography showed no significant stenosis, but left ventriculography demonstrated apical asynergy with basal hyperkinesia (apical ballooning). A striking filling defect highly suggestive of a thrombus was also viewed at the apex (panel A, diastole; panel B, systole; and video 1, white arrows; to see video footage visit the *Heart* website—http://heart.bmj.com/supplemental). Left ventricular ejection fraction was 40%. The apical ballooning and intraventricular thrombus were confirmed by transthoracic echocardiography. The patient was discharged under anticoagulant treatment.

After 2 months the ECG showed normal findings, and a transthoracic echocardiogram showed absolutely normal left ventricular (LV) wall motion and complete resolution of the apical thrombus.

Direct evidence of a LV thrombus associated with takotsubo-like ventricular dysfunction has not been demonstrated, although there have been reports regarding the embolic complications of this disorder.



End diastolic (panel A) and end systolic (panel B) ventriculograms of the patient, showing aquinesia of apical segments of the left ventricle (LV) and hypercontraction of basal and mid segments. A striking filling defect highly suggestive of a thrombus was also viewed at the apex (white arrow). Ao, aorta.

Some articles reported that the akinetic LV wall in the setting of myocardial infarction is an important cause of LV thrombus. Given that the LV thrombus in the present case was caused by a wall motion abnormality, its clinical appearance seems rather late. We report a case of transient LV apical ballooning with LV thrombus demonstrated in the early angiographic procedure. With restoration of LV apical wall motion and warfarin treatment, the LV thrombus disappeared. LV thrombus should be considered an early and delayed complication of transient LV apical ballooning.

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To view video footage visit the *Heart* website—http://heart.bmj.com/supplemental