LETTERS

Echocardiography of pulmonary vascular function in asymptomatic carriers of *BMPR2* mutations

To the Editors:

Pulmonary arterial hypertension (PAH) is a rare, life-threatening dyspnoea–fatigue syndrome, caused by progressive increase in pulmonary vascular resistance (PVR) and eventual right ventricular failure [1]. The heritable form of PAH has been shown to be associated with mutations of the gene encoding the bone morphogenetic protein receptor-2 (*BMPR2*). Asymptomatic carriers of *BMPR2* mutations are at high risk of developing PAH [2]. Careful follow-up of these subjects might help to detect early-stage disease with a more favourable response to targeted therapies. However, there is uncertainty about the optimal screening method. A recent European multicentre study showed that relatives of patients with idiopathic PAH (IPAH) present with an increased prevalence of abnormally high pulmonary artery pressure (PAP) during exercise or during low-oxygen breathing [3]. In that study, measurements of pulmonary vascular function were limited to a systolic PAP (sPAP) estimated from the maximum tricuspid regurgitation velocity (TRV) assessed by Doppler echocardiography. Here, we report on additional measurements performed in one of the participating centres, providing insight into abnormal pulmonary vascular distensibility and hypoxia-induced PVR in healthy *BMPR2* carriers.

This study was part of a larger multicentre European project, which included 291 relatives of 109 IPAH patients and 191 age-matched controls [3]. The participating PAH centre in Brussels, Belgium, contributed with 35 relatives of 10 index patients with IPAH and 38 healthy controls. The 35 relatives were aged mean$\pm$SD 35 ± 14 yrs. The 38 controls were aged mean$\pm$SD 36 ± 10 yrs, and matched for sex and body surface area. Five of the asymptomatic relatives and two of the index IPAH patients were carriers of *BMPR2* mutations. All relatives and controls underwent complete standard Doppler echocardiography at rest, followed by repetitive measurements of sPAP during exercise, with workload increased by 25 W every 2 min up to the maximum tolerated, and after 2 h of breathing an inspiratory oxygen fraction of 0.12, as previously described [3]. sPAP was calculated from maximum TRV [4].

Additional analysis specific to this study consisted of right ventricular outflow tract time–velocity integral ($RVOT_{VTI}$) during the resting normoxic and hypoxic measurements, to estimate a mean PAP (mPAP) from the acceleration time of pulmonary flow velocity [5], and PVR calculated as $10 \times$ TRV/$RVOT_{VTI}+0.16$ Wood units [6]. mPAP was also calculated from sPAP using the formula mPAP$=0.6 \times$ sPAP$+2$ mmHg [7]. Cardiac output (Q) was estimated from the left ventricular outflow tract (LVOT) diameter, $LVOT_{VTI}$ and cardiac frequency (fC) at rest [8], and exercise–associated changes estimated from proportional changes in fC. Linear regressions were calculated

on multipoint mPAP–Q plots, with adjustment for individual variability [9]. As multipoint mPAP–Q relationships actually disclose a slight curvilinearity, a distensibility coefficient α accounting for it was calculated using the equation mPAP$=(((1+\alpha \times \text{LAP})^5+5\alpha R_0 Q)^{1/5}-1)/\alpha$, where R_0 is total PVR at rest and LAP is left atrial pressure, which is assumed to be unchanged from the resting state, as previously described [9]. Data are presented as mean$\pm$SD. The statistical analysis consisted of a repeated-measures ANOVA and modified paired t-tests when the F-ratio of the ANOVA reached a critical p<0.05 value.

The main results with measurements at rest, at the maximum workload achieved and after 2 h of hypoxia, are shown in table 1. Maximum workloads were 103 ± 45 W in the *BMPR2* carrier relatives, 113 ± 38 W in the non-*BMPR2* carrier relatives and 119 ± 33 W in the controls. Resting mPAP calculated from TRV or from the acceleration time of $RVOT_{VTI}$ were not different: 14 ± 2 *versus* 12 ± 6, 15 ± 2 *versus* 14 ± 3 and 15 ± 3 *versus* 15 ± 3 mmHg in normoxia, and 28 ± 5 *versus* 29 ± 5, 27 ± 5 *versus* 25 ± 6 and 25 ± 4 *versus* 22 ± 5 mmHg in hypoxia in *BMPR2* carrier relatives, non-*BMPR2* carrier relatives and controls, respectively (p-values were always nonsignificant between the two methods). Blood pressure, fC, mPAP, Q, PVR and the slopes of mPAP–Q relationships were not different between the three groups. PVR did not decrease during exercise in the *BMPR2* carriers. Individual mPAP–Q relationships showed a marked interindividual variability (fig. 1). However, α was markedly decreased in the *BMPR2* carriers, at rest and during exercise. Furthermore, the *BMPR2* carriers also had an enhanced hypoxic pressure response when expressed as PVR *versus* arterial oxygen saturation measured by pulse oximetry. Hypoxia was associated with a decrease in α, which was of the same magnitude in the three study groups. There was a correlation between mPAP after 120 min of hypoxia and at maximal exercise (r=0.49, p<0.001).

The present results show the potential relevance of refined analysis of stress echocardiography PAP responses to exercise and hypoxia in terms of pressure–flow relationships and PVR–S_{P,O_2} plots. Previous invasive studies have shown that multipoint mPAP–Q relationships conform to a distensible mathematical model of the pulmonary circulation better than the PVR equation [10]. Thus, adding a measure of the compliance of pulmonary resistive vessels allows for an improved prediction of pressures at given levels of flow. It is interesting that α calculated at 2% change in diameter per mmHg transmural pressure from invasively as well as noninvasively measured multipoint pressure–flow plots agrees with *in vitro* measurements in isolated arterioles [9, 10]. Whether decreased α in the asymptomatic *BMPR2* mutation carriers in the present study reflects early pathological changes with potential for progression is not known.

TABLE 1	Haemodynamic measurements at maximal exercise and after 2 h of hypoxic breathing in asymptomatic carriers of bone morphogenetic protein receptor-2 mutations (BMPR2+), healthy relatives of patients with pulmonary arterial hypertension (BMPR2-) and controls		
	Rest	**Exercise**	**Hypoxia**
fC beats·min⁻¹			
BMPR2+	74 ± 9	$136\pm15^{+}$	$94\pm9^{\S}$
BMPR2-	67 ± 15	$135\pm20^{+}$	$85\pm21^{\S}$
Controls	74 ± 11	$132\pm17^{+}$	$84\pm13^{\S}$
mPAP# mmHg			
BMPR2+	14 ± 2	$25\pm3^{+}$	$28\pm5^{\S}$
BMPR2-	15 ± 2	$22\pm7^{+}$	$27\pm5^{\S}$
Controls	15 ± 3	$21\pm7^{+}$	$25\pm4^{\S}$
Q L·min⁻¹			
BMPR2+	6.2 ± 1.0	$11.3\pm1.5^{+}$	7.4 ± 1.6
BMPR2-	5.5 ± 1.7	11.3 ± 4.6	$6.4\pm1.7^{\S}$
Controls	5.6 ± 1.2	$11.1\pm2.7^{+}$	$6.8\pm2.2^{\S}$
TPVR Wood units			
BMPR2+	2.5 ± 0.4	2.2 ± 0.3	$3.8\pm1.2^{\S}$
BMPR2-	2.8 ± 0.9	$2.1\pm0.9^{+}$	$3.9\pm1.9^{\S}$
Controls	2.8 ± 0.8	$2.1\pm0.9^{+}$	$3.6\pm1.9^{\S}$
TPVR/S_{P,O_2} Wood units·%⁻¹			
BMPR2+	0.013 ± 0.002		$0.033\pm0.004^{*,\P,\S}$
BMPR2-	0.014 ± 0.002		$0.028\pm0.004^{\S}$
Controls	0.014 ± 0.003		$0.028\pm0.004^{\S}$
α %·mmHg⁻¹			
BMPR2+	$1.8\pm0.5^{*,\P}$	$1.0\pm0.3^{*,\P,+}$	$1.0\pm0.3^{\S}$
BMPR2-	3.4 ± 0.4	$1.5\pm0.4^{+}$	$1.0\pm0.2^{\S}$
Controls	2.9 ± 0.4	$1.4\pm0.2^{+}$	$1.0\pm0.1^{\S}$
Mean α %·mmHg⁻¹			
BMPR2+		$1.2\pm0.4^{*}$	
BMPR2-		2.1 ± 0.2	
Controls		1.5 ± 0.9	
mPAP–Q slope mmHg·L⁻¹·min			
BMPR2+		1.50 ± 0.4	
BMPR2-		1.75 ± 0.6	
Controls		1.71 ± 0.6	

Data are presented as mean± SD. fC: cardiac frequency; mPAP: mean pulmonary artery pressure; Q: cardiac output; TPVR: total pulmonary vascular resistance; S_{P,O_2}: arterial oxygen saturation measured by pulse oximetry; α: distensibility coefficient (in % diameter change per mmHg pressure). #: calculated from tricuspid jet velocity. *: p<0.05 for BMPR2+ versus BMPR2-; ¶: p<0.05 for BMPR2+ versus controls; +: p<0.05 for exercise versus rest; §: p<0.05 for hypoxia versus rest.
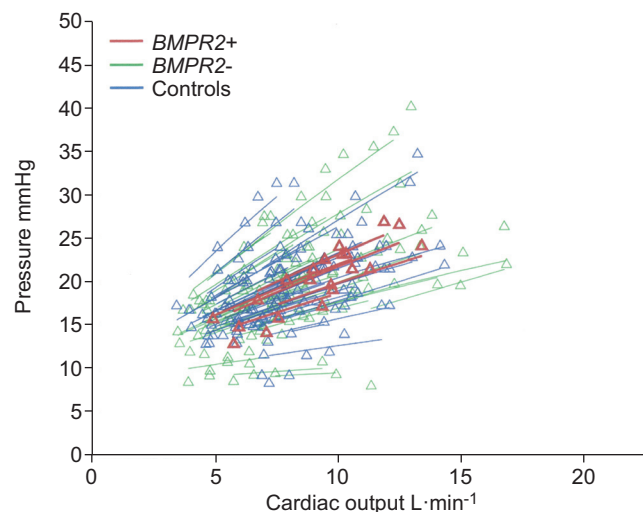

FIGURE 1. Individual multipoint mean pulmonary artery pressure–cardiac output plots, fitted using distensible models of the pulmonary circulation. The responses were variable, and similar in bone morphogenetic protein receptor-2 mutations (BMPR2+), healthy relatives of patients with pulmonary arterial hypertension (BMPR2-) and controls.

There are obvious limitations to the present preliminary report. The number of healthy BMPR2 mutation carriers was small, and pressure and flow calculations from noninvasive measurements rested on several assumptions. IPAH is a rare disease, with an incidence of one to two cases per million per year, only a minority of these patients is carrying a BMPR2 mutation, and asymptomatic relatives carrying a BMPR2 mutation are difficult to identify [1–3]. Exercise stress echocardiographic estimates of PAP and Q have previously been reported to be associated with realistic α calculations [9]. Left atrial pressure was not measured, but assumed constant, in keeping with previous estimates in normal subjects at exercise [9] and invasive studies showing that significant increases in LAP occur at exercise only at high workloads >150 W associated with cardiac outputs over 15–20 L·min⁻¹, much higher than in the present study [12]. The assumption in the present study that fC would be the main determinant of exercise-induced increase in Q may be more debatable. We therefore compared distensibility α and Q calculated from changes in fC only or from repetitive LVOT$_{VTI}$ and fC measurements during exercise stress echocardiography in a total of 20 healthy subjects included in a recently reported study [13]. The results of both methods were highly correlated. The fC-only method underestimated Q only at values >15 L·min⁻¹ and α was underestimated by ~10 %.

It is hoped that the present echocardiographic approach for the study of pulmonary vascular function will be applied with more direct measurements and further validation in future studies on patients with risk factors for the development of PAH.

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Our data also show that healthy BMPR2 mutation carriers present with an enhanced hypoxic pressure response to hypoxia. This result agrees with recent report that BMPR2 mutant mice are more susceptible to hypoxic pulmonary hypertension [11]. Hypoxic breathing was associated with the expected decrease in α in the three study groups [10], suggesting that any intrinsic difference in pulmonary vascular compliance is overwhelmed by hypoxic pulmonary vasoconstriction.

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Diabetes is a risk factor for tuberculosis in the Inuit population of Greenland

To the Editors:

Diabetes is a known risk factor for tuberculosis (TB), and studies across populations and geographic regions suggest substantial increased risks of developing TB ranging from 1.16 to 7.83 with co-existing diabetes [1]. It is suggested that the risk is due to latent TB infections being activated by the hyperglycemia associated with diabetes. The evolving epidemiology of concurrent diabetes and TB in settings where both diseases are frequent is therefore looked upon with special concern. The prevalence of diabetes among the Greenland Inuit is high (10%) and increasing [2]. Meanwhile, the TB incidence remains high with an estimated 180 cases per 100,000 suggesting ongoing TB transmission [3]. The aim of this study was to quantify the effect of diabetes on TB development among the Greenland Inuit.

We conducted a retrospective cohort study. Study participants comprised ethnic Inuit who participated in two previously conducted cross-sectional studies where diabetes status were assessed; Inuit Health in Transition Study (IHIT) [4] and the Greenland Population Study (B99) [2]. All study participants in

IHIT and B99 were randomly selected from the Civil Registration System (CRS) in order to represent the entire Greenlandic population. The CRS provides all citizens of Greenland with a unique identification number at birth, facilitating tracing of persons through all public registries. The CRS identifier enabled follow-up of study participants in the National TB register. The study was approved by the Ethics Review of Greenland.

Participants not previously diagnosed with diabetes (98%) underwent a standard oral glucose tolerance test (OGTT). Participants were categorised with diabetes if previously diagnosed with diabetes or if fasting and 2-h blood glucose levels were $\geqslant 7$ mmol·L^{-1} and $\geqslant 11.1$ mmol·L^{-1}, respectively. Weight and height were measured and body mass index (BMI) calculated. Age and sex of participants were determined from CRS data. Place of residence, divided into town or settlement, was likewise derived from the CRS registry.

TB is a mandatory notifiable disease in Greenland and all incident cases diagnosed by a medical doctor are recorded in the National TB register [5]. For the present study, all incident