Letter to Editor

Myocardial fibrosis in stroke survivors

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Stroke survivors are most likely to die of cardiac death, yet few undergo comprehensive cardiac assessment to look for reversible causes. Myocardial fibrosis (MF) is not only the hallmark of cardiomyopathy, but also a substrate for sudden cardiac death, ventricular tachyarrhythmia and heart failure. Procollagen carboxyl-terminal telopeptide (PICP) was found to be a marker of MF. The relationship between PICP and cardiac abnormalities in stroke survivors is unknown. We recently showed that MF in stroke survivors can be treated by spironolactone and amiloride in a randomised placebo-controlled cross-over study with reduction in PICP levels and QTc [1].

Querejeta et al. found that serum PICP was significantly higher in patients with severe fibrosis, as identified by histological assessment of biopsied myocardial tissue, than in patients with less severe fibrosis (140 ± 13 μg/L vs 108 ± 6 μg/L) [2][10]. A cut-off value of 127 μg/L for PICP was 78% specific and 75% sensitive at predicting severe fibrosis with a relative risk of 4.8 (95% CI, 1.19 to 19.30)[10].

Herein, we aim to determine the prevalence of severe MF in stroke survivors, as evidenced by Procollagen carboxyl-terminal telopeptide (PICP) > 127 μg/L (specificity: 78%, sensitivity: 75%). We also tested the hypothesis that PICP is associated with reversible cardiac pathologies in stroke survivors.

Stroke survivors who made a good recovery and were at least one month after a recently documented stroke or transient ischaemic attack (TIA) were recruited into the study. A random sample of the stroke outpatient clinic was recruited and this comprised 70% who had been hospitalised within 72 h following their acute cerebrovascular event plus 30% who suffered community strokes.

Patients who were known to have liver or lung fibrosis or recent surgery (within last 6 months), those who were unable to consent e.g., due to dementia; patients who were living in nursing home and those over 90 years of age and those with atrial fibrillation were excluded at recruitment.

Myocardial perfusion imaging was performed using dipyridamole as stressor. Ejection fraction was determined using GATED SPECT. Left ventricular mass index (LVMI) was determined by echocardiography. The concentration of PICP and Brain natriuretic peptide (BNP) was measured by radioimmunoassay. QTpc of lead I and QT dispersion were obtained from a 12-lead ECG.

Variables were reported as mean (SD)/median (interquartile range, IQR). One-sample Kolmogorov–Smirnov Test assessed if the residuals were normally distributed. Statistical significance was determined by Independent T/Chi-squared/Mann–Whitney U and the Mantel–Haenszel Common Odds Ratio was assessed and reported with 95% confidence interval (CI).

Ethical approval was obtained from the Tayside Committee on Medical Research Ethics. The study also had ARSAC approval. All patients gave informed consent to the study.

186 stroke survivors were studied. Severe myocardial fibrosis is prevalent amongst stroke survivors. 36% (67 out of 186) had PICP > 127 mcg/L.

Table 1 shows the clinical characteristics of the patients, classified according to the severity of myocardial fibrosis. Stroke survivors with severe fibrosis were older [68 (8) vs 65 (10), p = 0.049]. There was a weak correlation between PICP

and age as a continuous variable (r = 0.2, p = 0.011).

Table 1 Clinical parameters classified according to the severity of myocardial fibrosis.

	With non-severe fibrosis (PICP < or = 127 mcg/L)	With severe fibrosis (PICP > 127 mcg/L)	p
Age	65 (10)	68 (8)	0.049*
Sex (male/female)	72/47	39/28	0.8
Systolic BP	144 (20)	144 (19)	0.99
Diastolic BP	80 (11)	79 (10)	0.4
LVMI	100 (48)	110 (48)	0.2
EF (gated SPECT nuclear scan), %	55 (12)	58 (10)	0.3
BNP, pg/ml	15 (IQR 10–22)	15 (IQR 10–24)	0.8
Myocardial perfusion (score at rest)	63 (IQR 61–64)	63 (IQR 62–64)	0.17
Inducible ischaemia score	0 (IQR 0–4)	0 (IQR 0–3)	0.79

Stroke survivors with severe fibrosis had similar blood pressure (144/79 mm Hg in severe fibrosis patients, vs 144/80 mm Hg), history of angina or myocardial infarction and degree of inducible ischaemia (0, interquartile range (IQR) = 0–3, vs 0 (IQR 0–4), p = 0.79) when compared with those with lower PICP levels.

There was a very weak correlation between PICP and left ventricular mass index as continuous variables [r = 0.2, p = 0.011]. However, there is no relation between significant left ventricular hypertrophy (LVH) and severe myocardial fibrosis (Fisher's exact test P = 0.3) [Fig. 1].
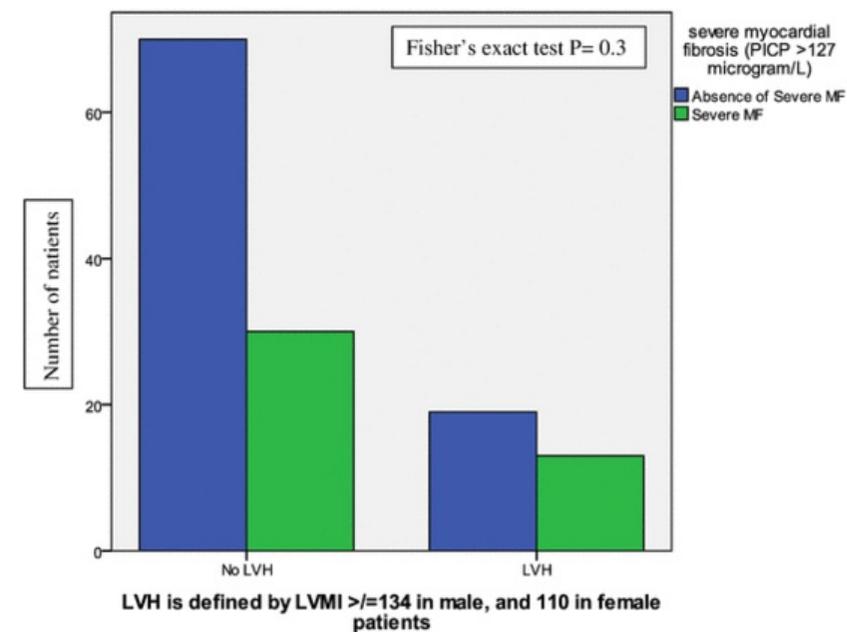
Fig. 1 Significant LVH is not associated with severe myocardial fibrosis.

No correlation was found between PICP and ejection fraction (in the 52 patients who had gated SPECT scan) or BNP levels at rest (Spearman p = 0.3, N = 179). Fig. 2 confirms the lack of relation between severe myocardial fibrosis and BNP. Further, no correlation was found between PICP and QT dispersion (Table 2).
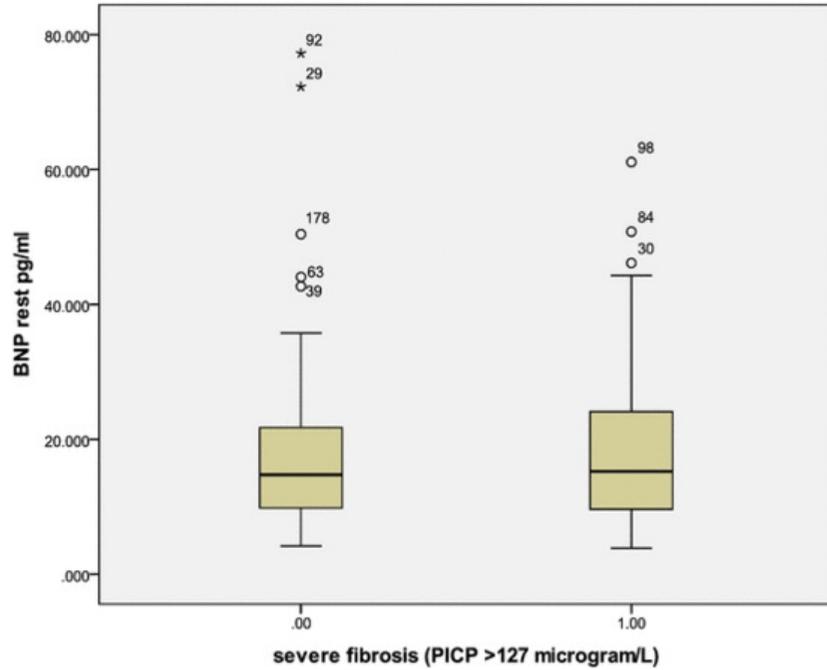
Fig. 2 Box plot showing that severe myocardial fibrosis was not associated with increased BNP levels at rest.

Table 2 Myocardial fibrosis was not associated with longer QT dispersion.

	With non severe fibrosis (PICP < or = 127 mcg/L)	With severe fibrosis (PICP > 127 mcg/L)	p
QT dispersion, ms	59 (23)	56 (18)	0.3
QTpc of lead I, ms	327 (23)	320 (21)	0.08

The key finding of the present study is that severe myocardial fibrosis is prevalent in stroke survivors. Stroke survivors are at highest risk of cardiac death. Severe myocardial fibrosis, as measured by PICP, has been shown to be treatable [1], but up until now, PICP is rarely measured in stroke survivors.

In conclusion, myocardial fibrosis is prevalent in stroke survivors who are at higher risk of cardiac death. Whilst a statistically significant association was found between MF and LVMI, the correlation is very weak. The hallmark features of pathological LV hypertrophy are myocyte hypertrophy and myocardial fibrosis, but patchy fibrosis can precede the development of overt hypertrophy as evidenced in an elegant cardiac MRI study in patients with hypertrophic cardiomyopathy [3]. As myocardial fibrosis was shown to be treatable, further research should test the hypothesis that reducing myocardial fibrosis in stroke survivors would translate to improved cardiac survival.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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[1]

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