Indian Heart Journal 70 (2018) 282–288

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

The effect of percutaneous coronary revascularization on plasma N-terminal pro-B-type natriuretic peptide levels in stable coronary artery disease

Amit Gupta[a], Jahangir Rashid Beig[a,*], Nisar A. Tramboo[a], Dil Afroze[b], Imran Hafeez[a], Hilal A. Rather[a]

[a] Department of Cardiology, SKIMS, Srinagar, India
[b] Department of Immunology, SKIMS, Srinagar, India

ARTICLE INFO

Article history:
Received 9 December 2016
Accepted 10 August 2017
Available online 16 August 2017

Keywords:
Coronary artery disease
Chronic stable angina
NT-ProBNP
Percutaneous coronary revascularization

ABSTRACT

Background: This study was conducted to assess the effect of percutaneous coronary revascularization (PCR) on plasma NT-proBNP concentration in patients with chronic stable angina (CSA).
Methods: This prospective open label interventional study included 22 patients with moderate to severe CSA, normal left ventricular (LV) systolic functions and critical (>90%) proximal stenosis in one of the three major epicardial coronary arteries. After stabilization of medications for 8 weeks, resting supine plasma NT-proBNP levels were measured and patients underwent PCR of the involved vessels. Eight weeks later, with medications unaltered; plasma NT-proBNP levels were repeated and compared with the baseline levels. LV systolic and diastolic functions were assessed before and after PCR.
Results: The mean age of the patients was 61.27 ± 8.87 years. Out of 22 patients, 20 were male and 2 were female. PCR was performed on left anterior descending coronary artery (LAD) in 12 patients and in a non-LAD vessel in 10 patients. After 8 weeks of successful PCR, there was a significant overall reduction in mean plasma NT-proBNP levels (from 244.36 ± 218.99 to 168.68 ± 161.61 pg/mL, p = 0.016). The patients who underwent PCR of LAD demonstrated significantly reduced NT-pro-BNP levels after PCR ($p = 0.009$). In the non-LAD group, NT-proBNP levels also decreased, albeit insignificantly ($p = 0.432$). Reduction in NT-proBNP was independent of change in LV systolic functions.
Conclusion: Successful PCR, by relieving myocardial ischemia, significantly reduced plasma NT-proBNP levels in majority of the patients with chronic stable angina secondary to critical epicardial coronary artery stenosis.

1. Introduction

Coronary artery disease (CAD) is the leading cause of deaths worldwide.[1] Therefore, besides new avenues and concepts of primary prevention, improved secondary preventive strategies of CAD are necessary to reduce the burden of disease and its recurrent complications.

Chronic stable angina (CSA) is the initial manifestation of CAD in approximately one half of the patients and constitutes up to two-thirds of the patients that undergo percutaneous coronary revascularization (PCR) in Western countries.[2–4] Whereas the benefits of an early invasive approach are well established in patients with an acute coronary syndrome (ACS); in patients with stable CAD, the indication for coronary angiography and revascularization is linked to clinical symptoms and verification of inducible myocardial ischemia by exercise testing or imaging techniques. Since the fundamental component in the process of clinical decision making in patients with CSA is the presence and severity of myocardial ischemia, the implementation of an additional, cost-effective and generally available biomarker is highly desirable. Patients with CSA, in contrast to acute coronary syndromes, are poorly characterized in terms of biomarkers that may help in prognostication, selecting therapeutic approaches or

Abbreviations: CAD, coronary artery disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

* *Corresponding author at: Department of Cardiology, SKIMS, Soura, Srinagar, Jammu & Kashmir, 190011, India.
E-mail addresses: amitcardio12@gmail.com (A. Gupta), jahangir3582@gmail.com (J.R. Beig), drnisartramboo@gmail.com (N.A. Tramboo), afrozedil@gmail.com (D. Afroze), imihaf@gmail.com (I. Hafeez), eemaan3@yahoo.co.in (H.A. Rather).

http://dx.doi.org/10.1016/j.ihj.2017.08.005

titration of therapeutic agents. In this regard, the role of natriuretic peptides has and is being seriously explored.

The ventricular natriuretic peptides like brain natriuretic peptide (BNP) and amino terminal or N-terminal pro-B-type natriuretic peptide (NT-proBNP) are established biomarkers for diagnosis and risk stratification of patients with cardiovascular diseases.[5] Elevated concentrations are predictive of poor prognosis in a variety of cardiovascular diseases.[5,6] As a biomarker, NT-proBNP scores over BNP in terms of its superiority for predicting cardiovascular events or death. Additionally, its better in-vitro stability and higher plasma concentrations make it a more sensitive biomarker than BNP.[7,8]

BNP and NT-proBNP have been shown to predict cardiovascular (CV) mortality and other adverse CV outcomes in patients with acute myocardial infarction, non-ST elevation acute coronary syndrome, and stable CAD.[8–13] Therefore, it has been concluded that ischemic heart disease across its broad spectrum influences cardiac endocrine function independent of resting left ventricular (LV) function. A strong correlation exists between BNP/NT-proBNP and extent of reversible ischemia even in patients with normal LV functions.[14–18] Some studies have also suggested that significant coronary stenosis per se, may cause plasma natriuretic peptide elevation.[16,19–21] This association between CAD and BNP/NT-proBNP has been attributed to increased BNP gene expression and release by cardiomyocytes in response to ischemia.[22] Studies of PCR also support this idea, since BNP increases transiently during balloon inflation (when ischemia occurs) and later falls when the ischemia is resolved.[20] So it is suggested that ischemia itself, rather than changes in left ventricular wall stress secondary to ischemia, promotes the release of BNP, but the responsible mechanisms still remain to be fully elucidated.[23,24]

The NT-proBNP level is elevated in chronic stable angina, a condition characterized by transient ischemic episodes, and predicts the cardiovascular outcomes in such patients. So any medication or intervention which decreases NT-proBNP levels should logically improve the outcomes in such patients. The purpose of this study was to assess the effect of PCR on plasma NT-proBNP concentration in patients with chronic stable angina, secondary to critical epicardial coronary stenosis. To the best of our knowledge, there is only one such study published in literature so far.[25]

2. Patients and methods

This study was conducted over a period of 2 years in the Department of Cardiology, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, (www.skims.ac.in), a tertiary care hospital in the valley of Kashmir, India.

2.1. Study design

This study was a Prospective Open Label Interventional Study comparing the effects of PCR on plasma NT-pro-BNP levels in stable CAD.

2.2. Study population

The patients of chronic stable angina presenting to the outpatient clinic of the Department of Cardiology of SKIMS were screened. Those with moderate to severe symptoms [Canadian Cardiovascular Society (CCS) class II–IV] on optimal medical therapy (OMT) and positive stress test (exercise ECG, stress echocardiography, or stress nuclear imaging) for reversible myocardial ischemia were further subjected to the inclusion and exclusion criteria as mentioned below:

2.2.1. Inclusion criteria

Patients presenting with the following conditions were included in the study:

- Normal 12-lead ECG
- Normal resting left ventricular systolic functions (LV ejection fraction > 50%) and normal valvular functions on echocardiography.
- No previous history of ACS.
- Normal kidney function tests [estimated glomerular filtration rate (eGFR) > 90 mL/min].
- Angiographically critical (>90% stenosis by visual estimation of lesion diameter compared with the adjacent normal segment) single vessel disease with either proximal-mid LAD or proximal RCA or LCx involvement.

2.2.2. Exclusion criteria

Patients presenting with the following conditions were excluded from the study group:

- Advanced diastolic dysfunction (>Grade I) on echocardiography.
- Angiographically documented double or triple vessel disease, or left main coronary artery (LMCA) disease.
- Patients who were non-compliant with medications or whose medications were changed during the study period.
- Patients who were not willing to undergo PCR.

2.3. Study protocol

The study protocol was cleared by the Institutional Ethics Committee. After obtaining an informed consent, the cardiovascular medications of all patients were stabilized to prevent any possible effect on NT-proBNP concentrations. After stabilization of medications for a minimum 8 week period, each patient underwent a detailed echocardiographic examination (performed by an experienced cardiologist who was blinded to the clinical details of the patient) followed by diagnostic coronary angiogram (CAG). The angiograms were assessed by two independent interventional cardiologists who were blinded to the clinical details of the patients. Patients who fulfilled the angiographic criteria for the study were recalled after 2 weeks for undergoing PCR. A resting, supine plasma sample was collected from each patient, before shifting to catheterization lab, and stored at −30 °C for the measurement of plasma NT-proBNP levels. Patients subsequently underwent PCR (n = 22) and intracoronary stents (drug eluting) were deployed in all. Successful PCR was confirmed by repeat coronary angiography (residual stenosis <20%; and no procedural complications). Patients were prescribed clopidogrel (600 mg stat) before PCR, and were continued on 150 mg once daily for one week; followed by 75 mg once daily (this was the only medication change during the study). Eight weeks later, with medications unaltered; patients returned for a repeat echocardiography (by the same cardiologist who performed the initial echocardiogram); and resting supine plasma sample was taken and stored at −30 °C till the estimation of NT-proBNP levels. Left ventricular end-diastolic volume index, end-systolic volume index, mass, ejection fraction, diastolic parameters and left atrial (LA) volume were assessed before and after PCR.

2.4. NT-proBNP assay

The blood samples for NT-proBNP were collected after a 30 min supine rest in Ethylenediaminetetraacetic acid (EDTA) vacutainers and promptly centrifuged at 1550*g* for 10 min. After separation,

plasma aliquots were stored frozen at −30 °C until assayed. NT-proBNP measurements were performed on an automated analyzer (Roche Diagnostics, Mannheim, Germany). The samples were analyzed using a Roche Diagnostics Cobas^{R} NT-proBNP electrochemiluminescence immunoassay kit employing polyclonal antibodies recognizing epitopes located in the N-terminal part of NT-proBNP.

In the first step, biotin-labelled and ruthenium-labelled polyclonal sheep antibodies (binding to different regions of NT-proBNP) were combined with 20 μL of sample and incubated for 9 min. In the second step, streptavidin-coated magnetic microparticles were added and the mixture was incubated for further 9 min. Next, the reaction mixture was transferred into the measuring cell where the beads were captured on the surface of an electrode by a magnet. Unbound label was removed by washing the measuring cell. In the last step, voltage was applied to the electrode in the presence of a tri-propylamine (TPA)-containing buffer and the resulting electrochemiluminescent signal was recorded by a photomultiplier.

The measuring range of the assay was 5–35,000 pg/mL or 0.6–4130 pmol/L, therefore, no dilution of samples was required. The functional sensitivity of the assay i.e. the lowest analyte concentration that could be reproducibly measured with an intermediate precision coefficient of variation of 20% was 50 pg/mL.

2.5. Statistical analysis

Continuous data was expressed as mean (±SD), and categorical data as frequencies and percentages. Tests of normality like Shapiro–Wilk test and graphical (normal quartile plot) exploration were performed to assess the fit of NT-proBNP variables (before and after PCR) to log-normal distribution. These suggested good fit [Shapiro Wilk test for NT-proBNP (pre-PCR, $p = 0.012$; post-PCR, $p = 0.003$) and for log NT-proBNP (pre-PCR, $p = 0.326$; post-PCR, $p = 0.577$)] and in subsequent analyses, this distribution was taken. Analyses were carried out using log transform of NT-proBNP, and moreover changes in log NT-pro-BNP correspond to multiplicative changes in NT-pro-BNP itself.

Arithmetic and geometric means of NT proBNP were calculated before and after PCR. The significance of change in NT-proBNP and echocardiographic parameters were observed by applying Wilcoxon's signed-rank test (a non-parametric test for paired samples with distribution that was not normal). The change in log NT-proBNP was scored by paired *t* test. Mann–Whitney test (a non-parametric test for independent samples) was applied to compare plasma NT-proBNP levels in LAD and non-LAD vessels. For comparing the reduction in NT-proBNP after PCR in LAD *vs.* non-LAD, multivariate analysis was used. A *p*-value of less than 0.05 was considered statistically significant. The data analysis was performed using comprehensive statistical software i.e. Statistical Software of Social Sciences (SPSS version 20.0) Chicago USA for Windows.

3. Results

We enrolled 22 patients who satisfied the eligibility criteria over a period of 2 years in our study.

3.1. Patient characteristics

The mean age of the patients was 61.27 ± 8.87 years with a range of 41–74 years. Nineteen of the total 22 patients were more than 50 years. Out of 22 patients, 20 (90.9%) were male and 2 (9.10%) were female. The mean body mass index (BMI) of the patients enlisted for this study was 24.35 ± 3.09 kg/m^2 with range of 17.63–31.07 kg/m^2. In terms of CV risk factors, 15 patients had a history of smoking, 15 were hypertensive, 5 were diabetic, and 10 had dyslipidemia. As far as the treatment regimen was concerned, all 22 patients were on aspirin, beta-blockers and statins before PCR, 3 patients were on pre-procedure clopidogrel, 15 patients received Angiotensin converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARB), 12 took nitrates, 9 were on calcium channel blockers, 7 received diuretics, 4 were on ranolazine and 3 received nicorandil.

3.2. Echocardiographic data before and after PCR

Echocardiographic data (Table 1) revealed no significant change after PCR in LV ejection fraction, end systolic volume index (ESVI), end diastolic volume index (EDVI), LV mass index, or LA volume index. However, when ratio of e and e′ velocities of septal and lateral walls were compared pre and post PCR, it revealed a

Table 1
Comparison of Echocardiographic data before and after PCR.

Parameters	Mean ± SD		Paired difference ± S.D	95% C.I	*p* value
	Pre PCR	Post PCR			
EF (%)	68.64 ± 5.23	69.09 ± 5.17	−0.45 ± 2.74	−1.67 to 0.76	0.373
ESV (mL)	30.86 ± 10.52	31.00 ± 10.04	−0.14 ± 4.12	−1.96 To 1.69	0.930
ESVI (mL/m^2)	17.97 ± 5.95	18.11 ± 5.87	−0.14 ± 2.58	−1.28 to 1.00	0.975
EDV (mL)	96.55 ± 23.33	100.18 ± 24.71	−3.64 ± 9.65	−7.92 to 0.64	0.083
EDVI (mL/m^2)	56.29 ± 13.64	58.45 ± 14.59	−2.16 ± 5.86	−4.7 to 0.43	0.079
LV mass (gm)	180.41 ± 44.44	176.47 ± 45.39	3.93 ± 15.27	−2.83 to 10.70	0.317
LV mass index (gm/m^2)	104.49 ± 22.78	102.08 ± 22.37	2.41 ± 8.67	−1.42 to 6.26	0.262
LA volume (mL)	36.39 ± 5.27	36.25 ± 4.52	0.15 ± 1.68	−0.59 to 0.90	0.867
LA VI (mL/m^2)	21.24 ± 3.08	21.18 ± 2.81	0.06 ± 0.99	−0.37 to 0.50	0.949
e/a	0.99 ± 0.32	0.94 ± 0.26	0.05 ± 0.15	−0.02 to 0.12	0.168
DT (ms)	146.36 ± 31.35	159.64 ± 22.52	−13.27 ± 31.84	−27.23 to 0.69	0.060
IVRT (ms)	81.55 ± 17.63	79.14 ± 17.73	2.41 ± 20.83	−6.83 to 11.65	0.549
e/e septal	7.38 ± 1.50	6.62 ± 1.34	0.75 ± 1.65	0.02 to 1.49	**0.046**
e/e lateral wall	6.59 ± 2.24	6.07 ± 2.04	0.51 ± 1.09	0.03 to 1.00	**0.039**

Note: DT – Deceleration Time; EF – Ejection Fraction; ESV – End Systolic Volume; ESVI – End Systolic Volume Index; EDV – End Diastolic Volume; EDVI – End Diastolic Volume Index; e/e′ ratio – Ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; LV – Left Ventricle; LA – Left Atrium; LAVI – Left Atrial Volume Index; PCR – Percutaneous Coronary Revascularization; IVRT – Isovolumic Relaxation Time.
The values represented in bold are statistically significant.

significant decrease ($p = 0.046$ and $p = 0.039$, respectively) although values before and after PCR were both within normal range i.e. <8.

3.3. Effect of PCR on plasma NT-proBNP levels

The mean plasma concentrations of NT-proBNP before and after PCR are shown in Table 2. Overall, there was a significant reduction in NT- proBNP levels after PCR ($p = 0.016$, $z = -2.386$, $r = -0.50$). 16 out of 22 patients had a decrease in NT-proBNP levels while 5 had an increase and 1 patient had no change subsequent to PCR. Of the 5 patients in whom there was a post-PCR increase in NT-proBNP levels, 2 displayed LAD involvement, 2 exhibited RCA involvement and 1 revealed LCx involvement. One patient in whom there was no change had RCA disease (Fig. 1).

In terms of log transformed values, there was a significant decrease in log NT-proBNP values after PCR ($p = 0.003$). The geometric means of NT-proBNP levels pre and post PCR were 159.82 and 97.38 respectively, thereby demonstrating a geometric mean (G.M.) decrease of NT-proBNP by factor of 39.0%.

There was one participant with baseline NT-proBNP level >800 pg/mL which appeared to be an outlier. However, within the log-transformed data, we observed an appropriate fit on the normal distribution curve and thus it was perceived as dispensed with. Nevertheless, to ensure that our results might not be affected by an isolated case, we repeated our analysis after excluding this patient. The mean NT-proBNP levels again showed a statistically significant decrease after PCR as compared to levels pre-PCR (214.69 pg/mL *vs.* 161.7 pg/mL, $p = 0.03$). Similarly, log NT-proBNP levels also showed statistically significant decrease after PCR (4.99 *vs.* 4.52, $p = 0.006$). The mean decrease in log NT-proBNP was 0.47. So, we concluded that this single case did not appreciably affect our results.

3.4. Comparison of plasma NT-proBNP levels before and after PCR in LAD vs non- LAD groups

Out of the overall 22 patients, 12 underwent PCR of LAD and 10 had PCR done to non-LAD vessel i.e. either RCA or LCx (Table 3). The patients who underwent PCR to LAD demonstrated significantly reduced NT-proBNP levels after PCR ($p = 0.009$, $z = -2.51$, $r = -0.53$). In the non-LAD group, NT-pro-BNP levels also decreased, though this reduction was not statistically significant ($p = 0.432$, $z = -0.87$, $r = -0.19$).

The mean decrease in log NT-proBNP in LAD group was 0.61 ($p = 0.005$) corresponding to a geometric mean decrease of NT-proBNP by 45.91%. The mean decrease in log NT-proBNP in non-LAD consortium was 0.35 ($p = 0.19$) which was statistically inconsequential; however being in agreement to a geometric mean decrease of 29.71% in NT-proBNP (Table 4).

There was no significant difference in pre-PCR NT-proBNP values while assessing LAD and non-LAD groups [$U = 43.00$, $z = -1.12$, $r = -0.23$, $p = 0.283$]. Also the post-PCR values did not show any striking difference between two groups [$U = 38.00$, $z = -1.45$, $r = -0.31$, $p = 0.159$]. Evaluation of the reduction of NT-proBNP after PCR in LAD *vs.* non-LAD groups by multivariate analysis did not show any considerable difference in either groups ($F = 1.298$, $p = 0.296$).

Table 2
Plasma NT-pro-BNP (pg/ml) before and after PCR.

Parameter		Mean ± S.D.	Percentile			*p* value
			25th	50th	75th	
NT-proBNP (pg/ml)	Pre-PCR	244.36 ± 218.99	88.90	147.59	415.07	**0.016**
	Post-PCR	168.68 ± 161.61	34.46	118.00	274.25	
Log NT-pro-BNP	Pre-PCR	5.07 ± 1.03	4.49	4.99	6.03	**0.003**
	Post-PCR	4.58 ± 1.20	3.54	4.76	5.61	

Note: NT-ProBNP – N-Terminal Pro-B-Type Natriuretic Peptide; PCR – Percutaneous Coronary Revascularization.
The values represented in bold are statistically significant.

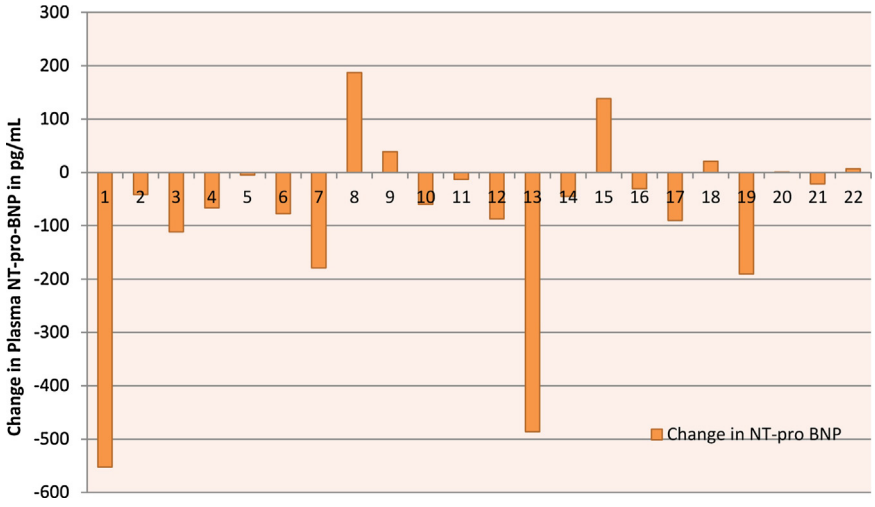

Fig. 1. Change in Plasma NT-pro-BNP in Individual Patients after PCR.

Table 3
Plasma NT-pro-BNP Levels before and after PCR in LAD *vs* non-LAD groups.

Vessel Involved	NT-pro BNP	Mean ± SD	Median	Mean Diff.	*z* score	*R*	*p*-value
LAD (n = 12)	Pre- PCR Post- PCR	216.71 ± 248.84 120.78 ± 119.83	136.90 77.22	95.93	−2.51	−0.53	**0.009**
Non-LAD (n = 10)	Pre- PCR Post-PCR	277.54 ± 184.32 226.15 ± 191.48	231.05 192.40	51.38	−0.87	−0.19	0.432

Note: LAD – Left Anterior Descending Coronary Artery; NT-ProBNP – N-Terminal Pro-B-Type Natriuretic Peptide; PCR – Percutaneous Coronary Revascularization.
The values represented in bold are statistically significant.

Table 4
Log NT-pro-BNP before and after PCR in LAD *vs* non-LAD groups.

Vessel Involved	Log NT-pro-BNP	Mean ± SD	Mean difference	p value
LAD (n = 12)	Pre PCR Post PCR	4.81 ± 1.18 4.19 ± 1.25	0.61 ± 0.62	**0.005**
Non-LAD (n = 10)	Pre PCR Post PCR	5.39 ± 0.76 5.03 ± 1.02	0.35 ± 0.78	0.190

Note: LAD – Left Anterior Descending Coronary Artery; NT-ProBNP – N-Terminal Pro-B-Type Natriuretic Peptide; PCR – Percutaneous Coronary Revascularization.
The values represented in bold are statistically significant.

4. Discussion

Our study revealed a significant fall in plasma NT-proBNP levels after successful PCR in majority of the patients with chronic stable angina secondary to critical stenosis of LAD, RCA or LCx coronary arteries. Previous studies have shown that percutaneous transluminal coronary angioplasty (PTCA) leads to acute transient increase in BNP levels.[20] In a recent study of 302 patients with stable CAD, Mehta et al. demonstrated that plasma NT-proBNP levels nearly doubled 12–24 h after PCR, compared to baseline values. They also found that other cardiac biomarkers including creatine kinase-MB, cardiac troponin T, and high sensitivity CRP showed a significant rise in the acute post procedural period suggesting procedure related subclinical myocardial damage as the reason for this rise in biomarker levels.[26] However, we were more interested in the longer term effect of ischemia resolution in ventricular derived natriuretic peptide levels. We chose an eight weeks stabilization period after PCR on the basis of acute temporal changes in plasma NT-proBNP levels demonstrated in previous studies of surgical and percutaneous revascularization, and to avoid confounding effect of restenosis and recurrent ischemia, which is a delayed phenomenon.[20,25,27] Drugs with potential to influence NT-proBNP levels were stabilized and maintained during the entire study period. McClure et al., in a study of 26 stable angina patients with normal LV systolic functions and isolated anatomic and physiologically significant stenosis [checked by fractional flow reserve (FFR)] of LAD coronary artery, documented a significant decrease in mean plasma NT-proBNP, 8 weeks after PCR. LAD was chosen in their study because of its major contribution to LV blood supply is most individuals. However, they did not provide any evidence for the mechanism causing NT-proBNP decrease, although indicating that it could be because of alteration of wall stress.[25]

In our present study we demonstrated a significant reduction in mean plasma NT-proBNP, 8 weeks after PCR (from 244.36 ± 218.99 pg/mL to 168.68 ± 161.61 pg/mL, p = 0.016). The mean decrease in log NT-pro-BNP was 0.496 which corresponds to the geometric mean decrease of NT-proBNP by 39%. In the absence of any significant change in LV ejection fraction (LVEF) after PCR, there could be two plausible reasons for the reduction of NT-proBNP levels. First, this could be related to improvement of LV diastolic functions. Second, it could be secondary to the resolution of ischemia per se. It is well established that BNP reliably detects the presence and severity of diastolic dysfunction.[28] Furthermore, ischemia is acknowledged as one of the cause leading to diastolic dysfunction.[29] Several studies have also shown that there is upregulation of ventricular BNP gene expression by myocardial hypoxia.[22,30] Although LVEF is an important predictor of mortality, the findings of studies by Ndrepepa et al. in CSA and by Omland et al. in ACS have shown that the association of BNP and all cause or cardiovascular mortality is independent of LVEF.[31,32] This suggests that natriuretic peptides provide information beyond LVEF. Elevation of ventricular natriuretic peptides may therefore be secondary to significant untreated CAD rather than LV dysfunction. In fact, studies have reported that BNP can detect silent myocardial ischemia in asymptomatic type 2 diabetes[33] and in stroke survivors.[14]

Our study added further to the McClure et al. report by including proximal RCA and LCx stenosis along with proximal and mid-LAD stenosis. When we subdivided our patients into LAD and non-LAD group, the LAD group showed a significant decrease in NT-proBNP levels (p = 0.009) with a mean decrease in log NT-prBNP of 0.61. The non-LAD group also demonstrated a decrease in NT-proBNP levels after PCR, although this decrease was not statistically noteworthy (p = 0.432). The studies by Weber et al. and Nishikimi et al. have shown that NT-proBNP levels correlate positively with the severity of CAD and proximal location of lesions, thereby indicating the area at risk of ischemia.[18,19] Hence, our results of statistically non-significant decrease is non-LAD group could have been because of relatively lesser area of myocardium supplied by RCA/LCx compared to LAD which subtends a much larger area of LV myocardium. Our study is the first to observe the effect of ischemia resolution on NT-proBNP levels in CSA patients in LAD as well as RCA/LCx coronary arteries. However, our cohort size was small which might also have affected the significance of the result and therefore will require larger studies to effectively ascertain this.

In this study, LV systolic and diastolic functions, before and after PCR, were also analyzed. We did not observe any significant change in LVEF, ESVI, EDVI and LV mass index. However, we did find that septal and lateral e/e′ velocity ratio significantly decreased after PCR although both pre-PCR and post-PCR values were within normal range. It is an established fact that e/e′ ratio <8 predicts a normal LV end diastolic pressure and LA pressure.[34] This significant decrease in e/e′ ratio was despite the fact that we had included patients with only mild diastolic dysfunction and excluded those with moderate to severe diastolic dysfunction from the study. LA volume index (LAVI) which normally decreases with improvement of diastolic parameters did not change significantly after PCR. So, it most certainly is the relief from myocardial ischemia, which either directly or indirectly by improving LV diastolic functions, that is

responsible for reduction in NT-proBNP levels. Whether this decrease in ventricular natriuretic peptides after resolution of ischemia translates into clinical benefits needs further deliberations.

The quest of accurately identifying patients with stable CAD who will derive benefit from revascularization over and above medical therapy is ongoing. In the landmark Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, PCR was not superior to optimal medical therapy (OMT) alone in stable CAD patients as far as hard clinical end points i.e. death, myocardial infarction (MI), stroke or hospitalization for ACS were concerned.[35] However, the COURAGE nuclear substudy showed that among patients who had moderate to severe pretreatment ischemia on myocardial perfusion single photon emission computed tomography (MPS), PCR in addition to OMT led to significantly lower unadjusted risk of death or nonfatal MI.[36] In a recent non-randomized study by Hannan et al., they found that most patients with stable CAD undergoing catheterization received PCR and those who received it experienced lower mortality, MI and revascularization rates.[37] A paper published by Bruyne et al. demonstrated that in patients with CSA and functionally significant stenosis, Fractional flow reserve (FFR) – guided PCR resulted in significant reduction in primary end point of death, MI or urgent revascularization.[38] The ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial is aimed at determining the best management strategy for higher risk stable CAD patients with at least moderate ischemia on stress imaging and its results will further enhance our understanding and implementation of management strategies. To our present understanding, PCR should provide mortality and morbidity benefit in stable CAD patients with significant ischemic burden. We believe that plasma NT-proBNP level might serve as a convenient and cost-effective biomarker to estimate the burden of myocardial ischemia in stable CAD; thereby providing more refined prognostication and aid in decision making process for revascularization in this patient population. Also, post-PCR reduction in NT-proBNP might serve as a surrogate marker of ischemia reduction in patients with elevated pre-PCR levels, thereby help in their post-procedural risk stratification. Lastly, we must keep in mind that measurement of natriuretic peptides to identify LV dysfunction might be significantly affected by the presence of occult ischemia in view of high prevalence of CAD.

5. Limitations

This study had some important limitations. First, the small sample size limits the accuracy of statistical methods and interpretation of our data. Second, we did not have a control group i.e. we did not assess change in NT-proBNP levels in matched subjects that were not subjected to PCR, because this was not ethically feasible. Third, the standard deviations in both pre PCI and post PCI NT-proBNP values were wide, especially considering the small study sample. This is because two patients in this study had NT-proBNP levels in the extremes of range before PCI (one had very high level of 867.40 pg/mL and the other had very low level of 15.69 pg/mL). Although we do not know the exact reason for these extreme levels, given the fact that all the patients had proximal single vessel disease and normal cardiac and renal functions, the variations in the NT-pro BNP levels may potentially be consequent to the medications that the patients were on before and after PCI. Fourth, although majority of the patients (16/22) experienced significant reduction in NT-proBNP, four patients had insignificant increase and one patient had marked increase in NT-proBNP levels after PCI. The reason for this rise in NT-proBNP levels remains elusive but could be secondary to procedure related factors (prolonged procedure time, multiple balloon inflations, larger contrast volume, slow flow etc.) which were not included in this study, and have been shown to be associated with acute post-PCI increase in BNP and NT-proBNP levels. Larger adequately powered studies are required to confirm these findings and to identify the predictors of change in NT-proBNP levels following PCI. Fifth, our patient group predominantly comprised of males. So, generalization of results to the whole population could be unfounded. Sixth, we did not check the physiological significance of coronary stenosis by FFR as this would have significantly added to the cost of procedure; considering our patients belonged to lower socioeconomic stratum and were not covered by insurance policies. However, all our patients had complete relief from angina post-PCR thereby indirectly reflecting a physiologically significant stenosis pre-PCR. Lastly, the follow up period in this study was very short. Therefore, long term follow up studies that include clinical end points may shed further light on whether these changes in plasma NT-proBNP levels translate into meaningful differences clinical outcomes.

6. Conclusion

The present study demonstrated that successful PCR, by relieving myocardial ischemia, significantly reduces plasma NT-proBNP levels in majority of the patients with chronic stable angina secondary to critical epicardial coronary artery stenosis. Larger studies with long term follow up are required to confirm these findings and to ascertain whether these changes in plasma NT-proBNP levels translate into meaningful differences clinical outcomes.

Source of funding

None.

Disclosure statement

The authors report no financial relationships or conflicts of interest regarding the content herein.

References

1. Mathers C, Fat DM, Boerma JT. *The Global Burden of Disease: 2004 Update*. World Health Organization; 2008.
2. Elvebac LR, Connolly DC, Melton LJ. Coronary heart disease in residents of Rochester, Minnesota,VII : incidence, 1950 through 1982. *Mayo Clin Proc*. 1986;61:896–900.
3. Kannel WB, Feinleib M. Natural history of angina pectoris in the Framingham study: prognosis and survival. *Am J Cardiol*. 1972;29:154–163.
4. Agema WR, Monraats PS, Zwinderman AH, et al. Current PTCA practice and clinical outcomes in The Netherlands: the real world in the pre-drug-eluting stent era. *Eur Heart J*. 2004;25:1163–1170.
5. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med*. 2004;350:655–663.
6. De Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med*. 2001;345:1014–1021.
7. Mishra RK, Regan M, Wu A, et al. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-ProBNP) vs. BNP for predicting adverse outcomes in patients with stable Coronary artery disease: the heart and soul study. *J Am Coll Cardiol*. 2012;59(13):E1412.
8. Richards AM, Nicholls MG, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. *Circulation*. 1998;97:1921–1929.
9. Mega JL, Morrow DA, De Lemos JA, et al. B-type natriuretic peptide at presentation and prognosis in patients with ST-segment elevation myocardial infarction: an ENTIRE-TIMI-23 substudy. *J Am Coll Cardiol*. 2004;44:335–339.
10. James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable Coronary artery disease a global utilization of strategies to open occluded arteries (GUSTO)-IV substudy. *Circulation*. 2003;108:275–281.

11. Morrow DA, de Lemos JA, Sabatine MS, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18. *J Am Coll Cardiol*. 2003;41:1264–1272.
12. Omland T, Sabatine MS, Jablonski KA, et al. Prognostic value of B-type natriuretic peptides in patients with stable coronary artery disease: the PEACE Trial. *J Am Coll Cardiol*. 2007;50:205–214.
13. Kragelund C, Grønning B, Køber L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med*. 2005;352:666–675.
14. Wong KY, McSwiggan S, Kennedy NS, et al. B-type natriuretic peptide identifies silent myocardial ischaemia in stroke survivors. *Heart*. 2006;92:487–489.
15. Davidson NC, Pringle SD, Pringle TH, et al. Right coronary artery stenosis is associated with impaired cardiac endocrine function during exercise. *Eur Heart J*. 1997;18:1749–1754.
16. Bibbins-Domingo K, Ansari M, Schiller NB, et al. B-type natriuretic peptide and ischemia in patients with stable coronary disease data from the Heart and Soul Study. *Circulation*. 2003;108:2987––2992.
17. Sadanandan S, Cannon CP, Chekuri K, et al. Association of elevated B-type natriuretic peptide levels with angiographic findings among patients with unstable angina and non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2004;44:564–568.
18. Weber M, Dill T, Arnold R, et al. N-terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris. *Am Heart J*. 2004;148:612–620.
19. Nishikimi T, Mori Y, Ishimura K, et al. Association of plasma atrial natriuretic peptide, N-terminal proatrial natriuretic peptide, and brain natriuretic peptide levels with coronary artery stenosis in patients with normal left ventricular systolic function. *Am J Med*. 2004;116:517–523.
20. Tateishi J, Masutani M, Ohyanagi M, et al. Transient increase in plasma brain (B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty. *Clin Cardiol*. 2000;23:776–780.
21. Heeschen C, Hamm CW, Mitrovic V, Lantelme NH, White HD. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Investigators. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. *Circulation*. 2004;110:3206–3212.
22. Goetze JP, Christoffersen C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J*. 2003;17:1105–1107.
23. Cantor WJ, Kim HH, Jolly S, et al. B-type natriuretic peptide and serum unbound free fatty acid levels after contemporary percutaneous coronary intervention. *J Invasive Cardiol*. 2008;20:186–188.
24. Yildirir A. Effects of lesion complexity on baseline and post procedural B-type natriuretic peptide levels in patients undergoing percutaneous coronary interventions. *Tex Heart Inst J*. 2007;34:282–289.
25. McClure SJ, Gall S, Schechter CB, et al. Percutaneous coronary revascularization reduces plasma N-terminal pro-B-type natriuretic peptide concentration in stable coronary artery disease. *J Am Coll Cardiol*. 2007;49:2394–2397.
26. Mehta V, Sukhija R, Mehra P, et al. Multimarker risk stratification approach and cardiovascular outcomes in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention. *Indian Heart J*. 2016;68:57–62.
27. Vanoverschelde JL, Depré C, Gerber BL, et al. Time course of functional recovery after coronary artery bypass graft surgery in patients with chronic left ventricular ischemic dysfunction. *Am J Cardiol*. 2000;85:1432–1439.
28. Grewal J, McKelvie R, Lonn E, et al. BNP and NT-proBNP predict echocardiographic severity of diastolic dysfunction. *Eur J Heart Fail*. 2008;10:252–259.
29. De Bruyne B, Bronzwaer JG, Heyndrickx GR, et al. Comparative effects of ischemia and hypoxemia on left ventricular systolic and diastolic function in humans. *Circulation*. 1993;88:461–471.
30. Ye W, Lee D, Chandrakala AN, et al. The expression of brain natriuretic peptide m-RNA is up-regulated in ischemic heart tissue in vivo and in vitro. *J Am Coll Cardiol*. 2012;59(13):E1398.
31. Ndrepepa G, Braun S, Niemöller K, et al. Prognostic value of N-terminal pro-brain natriuretic peptide in patients with chronic stable angina. *Circulation*. 2005;112:2102–2107.
32. Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation*. 2002;106:2913–2918.
33. Rana BS, Davies JI, Band MM, et al. B-type natriuretic peptide can detect silent myocardial ischaemia in asymptomatic type 2 diabetes. *Heart*. 2006;92:916–920.
34. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures a comparative simultaneous Doppler-catheterization study. *Circulation*. 2000;102:1788–1794.
35. Boden WE, O'rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.
36. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283–1291.
37. Hannan EL, Samadashvili Z, Cozzens K, et al. Comparative outcomes for patients who do and do not undergo percutaneous coronary intervention for stable coronary artery disease in New York. *Circulation*. 2012;125:1870–1879.
38. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001.