Validity of Cardiac Markers as Diagnostic and Prognostic Indicators of Complications in Patients undergoing Percutaneous Coronary Intervention

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Validity of Cardiac Markers as Diagnostic and Prognostic Indicators of Complications in Patients undergoing Percutaneous Coronary Intervention

*Hafidh A Alhadi[1] and Keith A A Fox[2]

مَصْدوقيَّة الواصمات القلبية كمؤشّرات تشخيصية ومحدّدات لمآل المضاعفات أثناء القسطرة العلاجية عبر الجلد

حفيظ الهادي، كيث فوكس

الملخص: **الهدف:** تقدير القيمة التشخيصية وتحديد المآل لبروتين حمض القلب الدهني الرابط أثناء القسطرة العلاجية المختارة عبر الجلد ومقارنته بالواصمات القلبية المعيارية **الطريقة:** أجريت دراسة استباقية على 80 حالة متعاقبة أدخلت المستشفى لإجراء قسطرة مختارة علاجية عبر الجلد. تم دراسة تركيز الواصمات القلبية: تروبونين القلب (ت)، تروبونين القلب (آي)، كتلة كاينيز الكرياتينين (م ب)، مايوجلوبين، و حمض القلب الدهني الرابط قبل القسطرة وبعدها بساعة، وساعتين وأربع ساعات وست عشرة ساعة وأربع وعشرين ساعة. ارتفاع تركيز الواصمات القلبية كان مرتبطا بمتغيرات ديموغرافية وأخرى تتعلق بالعملية والتصوير الشعاعي للأوعية.. تم متابعة المرضى لمدة 20 – 26 شهرا. **النتيجة:** بروتين حمض القلب الدهني الرابط كان الأسرع ارتفاعا و ذلك بعد ساعتين فقط من القسطرة، وكان الأنسب للتشخيص المبكر للجلطة القلبية للفترة من 1 – 3 ساعات بعد رأب الوعاء. ارتفعت الواصمات الأخرى بالنسب التالية: تروبونين القلب (آي) (46.25%)، مايوجلوبين (17.5%)، بروتين حمض القلب الدهني الرابط (13.3%)، كتلة كاينيز الكرياتين (م.ب) (11.25%)، و تروبونين القلب (ت) (7.5%). كان تروبونين القلب (آي) الأكثر حساسية لتشخيص كل المضاعفات و كان الأفضل بين الواصمات الأخرى. ارتبط ارتفاع الواصمات القلبية مع تقدم العمر (P<0.02)، والآلام الصدرية الحادة مع تغيرات نقص التروية في تخطيط القلب (P < 0.003)، واستخدام الدعامات (P > 0.019)، والمضاعفات الكبرى مثل التسليخ الرئيسي (P < 0.004)، وانسداد الوعاء المؤقت (P<0.022)، والدعامات العاطلة (P < 0.003)، وعند حدوث الجلطة القلبية (P < 0.042). ارتفاع الواصمات القلبية كان مترافقا مع انخفاض معدل البقاء بدون مضاعفات (16.92) شهرا مقارنة ب (20.67) شهرا(P < 0.03). **الخلاصة:** قد يكون باستطاعة بروتين حمض القلب الدهني الرابط التشخيص المبكر للجلطة القلبية بعد ساعة من حدوثها (أو بعدها). تروبونين القلب (آي) هو الأكثر قدرة على تشخيص المضاعفات الرئيسية أثناء القسطرة العلاجية. ننصح بأن يتم قياس تروبونين القلب (آي) بعد كل قسطرة علاجية بفترة (16 – 24 ساعة).

مفتاح الكلمات: القسطرة العلاجية، الجلطة القلبية، حمض القلب الدهني الرابط، الواصمات القلبية، تروبونين القلب.

ABSTRACT: ***Objectives:*** The aim of this study was to assess the diagnostic and prognostic value of heart-type fatty acid-binding protein (H-FABP) in elective percutaneous coronary intervention (PCI) and compare it with standard cardiac markers. ***Methods:*** A prospective evaluation was done of 80 consecutive patients admitted for elective PCI. Serum cardiac troponin T (cTnT), cardiac troponin I (cTnI), creatine kinase-MB (CK-MB mass), myoglobin, and H-FABP were determined pre-angioplasty and 1, 2, 4, and 16–24 hrs post-angioplasty. Elevated cardiac markers were correlated with demographic, angiographic and procedural variables. Patients were followed up for 20–26 months. ***Results:*** H-FABP peaked early at 2 hours and was useful for the early detection of evolving AMI within 1–3 hours after angioplasty. Cardiac-TnI, myoglobin, H-FABP, CK-MB mass, and cTnT concentrations were elevated in 46.25%, 17.5%, 13.3%, 11.25%, and 7.5% respectively. Cardiac-TnI was the most sensitive marker for detecting all complications and was superior to all other markers. Elevated cardiac markers were correlated with old age (P < 0.02); chest pain ± ECG changes of ischaemia (P < 0.003); use of stents (P < 0.019) and major complications such as major dissection (P < 0.004); transient vessel closure (P < 0.022); bail out stent (P < 0.003), and AMI (P < 0.042). Elevated cardiac markers were associated with a reduction of event-free survival (16.92 versus 20.67 months, P < 0.03). ***Conclusion:*** Heart-type-FABP measurements at 1 hour (or thereafter) post-PCI may offer an early chance of detecting evolving AMI; cTnI was the most sensitive marker for the detection of major complications in patients undergoing PCI. Measurements of cTnI 16–24 hours post-PCI should be part of the routine management of patients following elective PCI.

Keywords: Percutaneous coronary intervention; PCI; Acute coronary syndrome; Heart-type fatty acid-binding protein; Cardiac markers; Cardiac troponins; Complications.

[1]Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman; [2]University of Edinburgh Cardiovascular Research Unit, Royal Infirmary of Edinburgh, UK

To whom correspondence should be addressed. E-mail: halhadi@hotmail.com

Advances in Knowledge

1. *This article highlights the fact that the release of cardiac markers after percutaneous coronary intervention (PCI) is not uncommon and is associated with increased rate of future complications and reduction of event-free survival.*
2. *This article is the first of its kind to study the value of H-FABP in patients undergoing PCI and to evaluate its role in the diagnosis and prognosis of complications during and after PCI.*
3. *This study provided a standardised setting to compare and contrast the ability of the different cardiac markers available in clinical use today to detect myocardial damage post PCI.*

Application to Patient Care

1. *This study will help health care professionals select the most appropriate early test for the diagnosis of suspected AMI in patients with acute chest pain post PCI.*
2. *This article recommends the introduction into clinical practice of routine measurements of cTnI after all elective PCI procedures. This will guide the estimation of myocardial damage, which is sometimes not obvious clinically, and may guide further management with antiplatelet therapy.*

Percutaneous coronary intervention (PCI) is widely used in the treatment of many patients with stable angina, unstable angina (UA), recurrent angina after coronary artery bypass grafting (CABG), and acute myocardial infarction (AMI).[1-3] PCI is, in general, a safe procedure; however, occasionally complications occur, including AMI (3–5%),[1-2] emergency CABG (3–7%),[4] and death (0.9%).[5] These events are usually caused by extensive arterial dissection, intracoronary thrombosis, or both, with resultant vessel occlusion. Acute closure occurs in 2–8% of patients undergoing PCI.[6] In 75% of patients with abrupt closure, it occurs within minutes, in the other 25% it usually occurs within 24 hours.[7] Ultrasound imaging has shown that dissection of the arterial wall is detected in 50–80% of patients who have undergone successful PCI.[8] Other complications of PCI include coronary vessel rupture or injury, re-stenosis, arrhythmias, coronary artery spasm/elastic recoil, and embolism.[9] Side branch occlusion occurs in 5% of side branches that are adjacent to a dilated coronary stenosis.[10]

Uncomplicated angioplasty is not associated with any significant release of cardiac markers;[11] however, more sensitive cardiac markers have increased the numbers of patients diagnosed with myocardial injury after PCI. These infarclets have been associated with increased risk of future complications.[12-14] Minor increases of creatine kinase-muscle and brain (CK-MB) after an apparently successful coronary intervention have been reported in 11.5–26% of cases, and have been associated with an increased risk of cardiac death and AMI during follow-up.[12,15] Serum cardiac troponin I (cTnI) and cardiac troponin T (cTnT) elevations have been detected in 13–44% of patients undergoing PCI.[14,16-17] An increased cTnT concentration post-PCI has been correlated with a higher incidence of complex lesion morphology during angioplasty.[18]

Heart-type fatty acid-binding protein (H-FABP) has been found to be a useful early marker for the detection of myocardial injury.[19] The value of H-FABP as an early marker for the identification of myocardial damage during PCI has not yet been studied. The aims of the study were to examine the relation between elevations of cardiac markers post-PCI and complication rates during and after PCI and to determine whether elevated cardiac markers post-PCI are related to demographic, angiographic or procedural variables.

Methods

The study population consisted of a consecutive series of 80 patients recruited from the Cardiology Unit at the Royal Infirmary of Edinburgh over an eight month period in 2002. Ethical approval for the study was obtained from the local ethical committee and written informed consent was obtained from each patient. Thereafter, five serial blood samples were collected from each patient at 0 hour (base line concentration, pre-angioplasty) and at 1 hour, 2 hours, 4 hours and 16–24 hours after angioplasty. The study group consisted of patients who were referred for elective angioplasty for both stable angina pectoris and UA. Patients who had a non-elective angioplasty (e.g. rescue angioplasty, primary angioplasty, salvage angioplasty, or emergency angioplasty) were excluded from this study. Patients were categorised into two main groups according to the presence (cTnI positive) or absence (cTnI negative) of elevated cTnI concentrations ≥ 0.18 µg/L. The two groups were compared with respect to demographic, angiographic and procedural

Table 1: Demographic and angiographic data of patients with and without elevated serum cardiac troponin I (cTnI). Continuous variables are presented as mean ± SD and categorical variables are presented as percentages (in brackets).

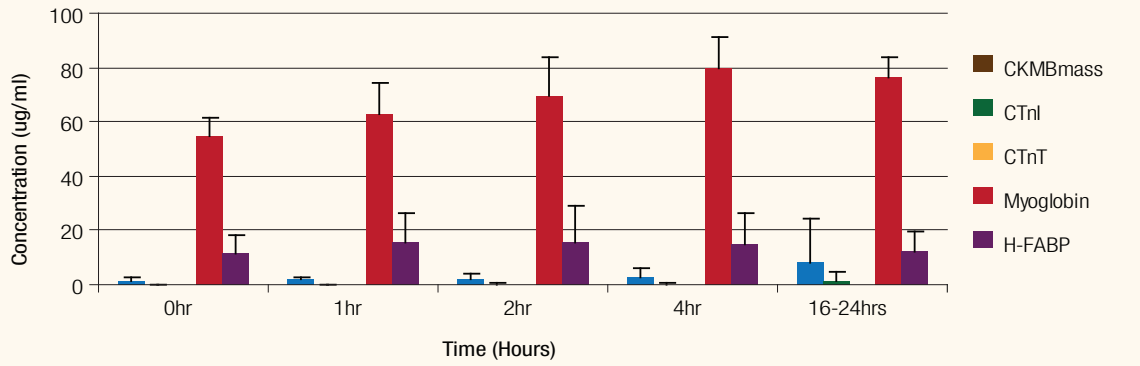
Demographic data	cTnI positive group (n = 37)	cTnI Negative group (n = 43)	*P* value
Age (yrs ± SD)	**64.35 ± 9.22**	**59.1 ± 7.47**	**0.02**
Male	26 (70)	33 (77)	NS
Female	11 (30)	10 (23)	NS
Type of preceding angina			
Stable angina	19 (51)	26 (43)	NS
Unstable angina	14 (38)	17 (40)	NS
Atypical angina	4 (11)	-	-
Risk Factors			
Smoking	24 (65)	27 (63)	NS
Diabetes Mellitus	3 (8)	8 (19)	NS
Hypercholestrolaemia	27 (73)	37 (86)	NS
Hypertension	18 (49)	14 (33)	NS
Family history of IHD	16 (43)	23 (53)	NS
Previous Cardiac Events			
Previous PCI	10 (27)	16 (37)	NS
Previous CABG	4 (11)	3 (7)	NS
Previous AMI	15 (41)	14 (33)	NS

Angiographic data	cTnI positive group (n = 37)	cTnI Negative group (n = 43)	*P* value
Type of CAD			
Single vessel CAD	6 (16)	14 (33)	NS
Multiple vessel CAD	31 (84)	29 (67)	NS
Anatomic site of PCI			
LAD	27 (73)	29 (67)	NS
LCX	11 (30)	14 (32)	NS
RCA	6 (16)	4 (9)	NS
Vein grafts	1 (3)	3 (7)	NS
Multiple vessel PCI	5 (14)	6 (14)	NS
Left ventricular EF (% ± SD)	62 ± 12	65 ± 14	NS
Clinical success)	27 (73)	41 (95)	0.013
Angiographic success	30 (81)	41 (95)	0.04

Legend: cTnI = cardiac troponin I; P = probability value; IHD = ischaemic heart disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; AMI = acute myocardial infarction; CAD = coronary artery disease; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; EF = ejection fraction;

variables, and the frequency of complications during PCI and the in-hospital period. Patients were followed-up for 20–26 months after discharge from hospital and the numbers of cardiac events in each group were compared. Angiographic success was defined according to the European Society of Cardiology Task Force Guideline on Angioplasty as < 20% residual diameter stenosis and thrombolysis in myocardial infarction (TIMI) 3 flow.[20] Clinical success was defined as angiographic success without in-hospital complications (death, AMI, emergency CABG, or ischaemia driven repeat PCI).

Cardiac-TnI, CK-MB mass, and myoglobin were analysed on a Stratus CS analyser machine (Dade Behring, Germany), using commercially available test materials. The coefficients of variations for cTnI were 6.8%, and 6.7% at concentration range 0.24–0.36µg/L, and 4.6–6.9 µg/L respectively. Heart-type-FABP was analysed by an enzyme linked immunosorbent assay method using commercially available assays (Hycult,



Legend: CK-MB = creatine kinase-muscle and brain mass; cTnI = serum cardiac troponin I; cTnT = serum cardiac troponin T; HFABP = heart-type fatty acid-binding protein

Figure 1: Serum cardiac markers before (0 hour), and at 1, 2, 4, and 16–24 hours after PCI in cTnI positive group. Data are presented as mean ± SD

Cambridge, UK). The analytical sensitivity of H-FABP mean ± 2SD was 0.206 ± 0.047 µg/L. Cardiac-TnT was analysed on Elecsys 2010 using commercial assays (Roche, Germany). The reference ranges quoted by the manufacturer for CK-MB mass, cTnI, myoglobin, cTnT, and H-FABP assays were validated by assaying the reference ranges of 20 healthy blood donors samples (10 males and 10 females, mean age ±SD = 63.8 ±8.01, range 53–75 years, median = 65 years). The mean ± SD concentrations of these markers were CK-MB mass =1.52 ± 0.8 µg/L, cTnI = 0.015 ± 0.006 µg/L, myoglobin = 41.5 ± 13.3 µg/L, cTnT = 0.011 ± 0.002 µg/L, and H-FABP = 6.86 ± 2.21 µg/L. The optimal cut-off concentrations of cardiac markers were based on receiver operating characteristic (ROC) curve analysis between patients with and without complications after PCI, and also considerations of cardiac markers concentrations in the normal healthy blood donor group, the control group, and the basal or pre-angioplasty concentrations. The following cut-off concentrations were used to indicate myocardial injury following angioplasty (cTnI ≥ 0.18 µg/L; cTnT ≥ 0.1 µg/L; CK-MB mass ≥ 5 µg/L; myoglobin ≥ 95 µg/L, and H-FABP ≥ 16 µg/L). All these cut-off concentrations were associated with statistically significant areas under the curve ($P < 0.0005$).

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS™, Pittsburgh, statistical software, Version 12). Continuous variables were presented as mean ± SD. Comparisons between cTnI positive and negative groups demographic, angiographic and procedural variables were conducted by the Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. Comparison of the mean concentrations of serial cardiac markers changes at 0 hour (before angioplasty) and at 1, 2, 4, and 16–24 hours after angioplasty was conducted by the Friedman test. Significance was defined as a P value ≤ 0.05. The rate of event-free survival was estimated from the Kaplan-Meier survival method and was compared with the log rank test.

Results

The study group included 21 females (26%) and 59 males (74%). The mean age of the group was 61.1 ± 7.5 years. The control group (who had an angiography procedure alone without angioplasty) consisted of 12 patients, 5 females and 7 males with a mean age 61.9 ± 8.7 years. There were no significant releases of any of the cardiac markers in the control group (data not shown). This provides evidence that excludes diagnostic procedure as the cause of cardiac trauma and supports angioplasty as the primary cause of cardiac markers release. Cardiac-TnI was the most frequent abnormal marker and was therefore chosen for comparison in this study. In 37 out of 80 patients (46.25%), the cTnI concentration was ≥ 0.18 µg/L. An increase in cTnI concentration (> 0.06– ≤ 0.17 µg/L) was observed in 22 patients (27.5%). The area under the curve (AUC) for cTnI was greater than that for other markers. Myoglobin was increased in 14 (17.5%) patients, H-FABP in 13.3%, and CK-MB mass in 11.25%. In all cases where CK-MB mass, cTnT, H-FABP or myoglobin were elevated, cTnI was also elevated.

Table 2: Procedural variables in patients with and without elevated cardiac troponin I (cTnI). Continuous variables are presented as mean ± SD and categorical variables are presented as percentages (in brackets).

Procedure data	cTnI positive group (n = 37)	cTnI Negative group (n = 43)	*P* value
Chest pain ± ECG changes of ischaemia	19 (51.4)	6 (13.9)	0.004
Procedure information			
Number of lesions dilated (per patient)	46 (1.24)	41 (1.24)	NS
Number of vessels dilated (per patient)	41 (1.11)	40 (1.21)	NS
Balloon diameter (mm)	3.3 ± 0.56	3.12 ± 0.45	NS
Total number of balloon inflation (n)	6.4 ± 4.6	4.81 ± 2.8	NS
Total time of balloon inflation (minutes)	3.77 ± 4.18	3.41 ± 2.86	NS
Maximum inflation time (seconds)	50.12 ± 26	55.24 ± 24.34	NS
Maximum inflation pressure (Pa)	11.21 ± 3.34	10.45 ± 3.56	NS
Total duration of procedure (minutes)	56.9 ± 38.3	42.31 ± 19.2	NS
Major complications during PCI			
Major dissection	10 (27)	1 (2)	0.004
Side branch occlusion	5 (13.5)	2 (5)	NS
Transient vessel occlusion	7 (19)	1 (2)	0.022
Major technical failure	1 (3)	0 (0)	NS
Bail out stent	7 (19)	0 (0)	0.003
Minor complications during PCI			
Minor dissection	8 (21.6)	7 (16)	NS
Coronary spasm/ elastic recoil	2 (5.4)	5 (12)	NS
Minor technical failure	1 (3)	2 (5)	NS
Post-procedural complications (24h)			
AMI	3 (8)	0 (0)	0.042
Angina with re-catheterisation	5 (13.5)	1 (2)	NS
Angina without re-catheterisation	1 (3)	2 (5)	NS
Emergency CABG.	0 (0)	0 (0)	-
Total number of stents	42	32	0.019
Reason for stenting			
Stent for dissection	15 (40.5)	8 (17)	0.05
Stent for sub-optimal result	12 (32.4)	15 (35)	NS
Elective stent	3 (8)	6 (14)	NS
Bail out stent	7 (19)	0 (0)	0.003
Use of IVUS during PCI	6 (16)	1 (2)	0.045
Post-procedural treatment			
Ticlopidine	11 (30)	20 (47)	NS
Clopidogrel	8 (22)	7 (16)	NS
Abciximab + Ticlopidine	3 (8)	2 (5)	NS
Abciximab + Clopidogrel	3 (8)	1 (2)	NS

Legend: cTnI = cardiac troponin I; P = probability value; ECG = electrocardiogram; NS = not significant; mm = millimetre; Pa = Pascal; PCI = percutaneous coronary intervention; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting

As compared with cTnI, cTnT was increased above the cut-off concentration in only 6 (7.5%) patients, and five of them had significant complications. Cardiac-TnT was elevated to concentrations between 0.01–0.06 µg/L in 36 patients, and between ≥ 0.06 – < 0.1 µg/L in 4 patients. The complications reported in these two groups were in 10 and 3 patients respectively. All 6 patients with cTnT > 0.1 µg/L and the 13 patients in the last two groups had cTnI ≥ 0.18 µg/L. In the cTnI negative group (43 patients, 53.75%), no increase in cTnT or CK-MB mass above the cut-off concentration was observed. Myoglobin was elevated in two patients, and H-FABP (concentration = 21 µg/L) in one

Table 3. Cardiac events during follow up for ≥ 20 months. Except where otherwise indicated, numbers in brackets indicate percentages.

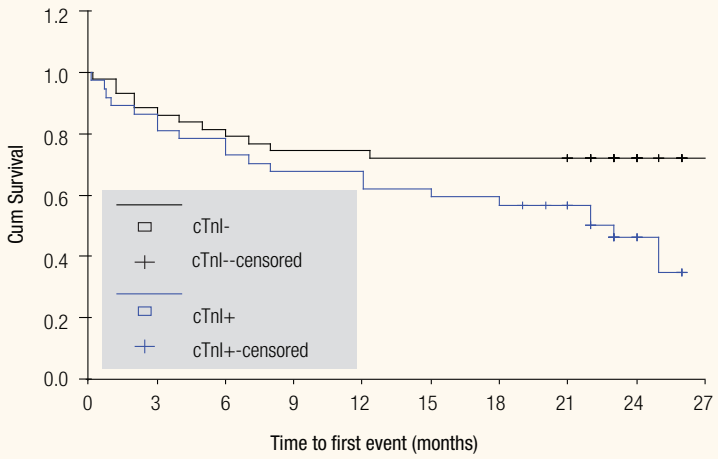
Events	cTnI (+) group (n = 37)	cTnI (-) group (n = 43)	*P* value
Angina control post-procedure			
Worse	10 (27)	10 (23)	NS
Better	20 (54)	30 (70)	NS
Unchanged	7 (19)	2 (5)	NS
Cardiac event(s) during follow-up			
Admitted with angina	5 (14)	3 (7)	NS
Admitted with UA	5 (14)	2 (5)	NS
Admitted with AMI	1 (3)	0	-
Admitted with Heart failure	1 (3)	0	-
Target vessel revascularisation	6 (16)	7 (16)	NS
Non-target vessel revascularisation	5 (14)	4 (9)	NS
Referred for CABG	3 (8)	3 (7)	NS
Death	1 (3)	2 (5)	NS
Total No. with uncontrolled angina	17 (46)	12 (28)	NS
Total No. of patients with events	17 (46)	12 (28)	NS
Total No. of events per group	29 (78)	21 (48)	NS
Average duration of follow-up (months)	22.6 ± 1.5	23 ± 1.2	NS
Patients lost to follow-up	0	1	

Legend: cTnI = cardiac troponin I; P = probability value; NS = not significant; UA = unstable angina; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting.

patient. The release patterns of cardiac markers in the cTnI positive group are shown in Figure 1. The peak concentrations of H-FABP, myoglobin, cTnI, cTnT, and CK-MB mass were achieved at 2 hrs, 4–16 hrs, 16–24 hrs, 16–24 hrs, and 16–24 hrs respectively.

Eighteen patients had an increase in cTnI concentration alone. Eight patients had some complications during PCI, whereas in 6 patients no specific complications were reported. However, in these patients the angioplasty was described as technically difficult and prolonged or the lesion was complex, and three patients had failure of stent deployment, sudden drop of blood pressure after sheath removal, and limb ischaemia post-procedure. Two patients in this group had total occlusion of the vessels and two had ostial lesions. In four patients with cTnI elevations (range 0.18–0.65 µg/L), no specific complications were reported to explain this rise.

The use of newer and potent antiplatelets treatment after PCI was liberal in this group of patients. Fifty-five patients (68%) received a combination of ticlopidine and/or clopidogrel and/or abciximab antiplatelets after stenting. The demographic and angiographic data of the cTnI positive and negative groups are shown in Table 1. Patients in the cTnI positive group were older ($P < 0.02$). Clinical and angiographic successes were reported more frequently in the cTnI negative group (95% versus 73%, $P < 0.013$), and (95% versus 81%, $P < 0.04$) respectively. Table 2 illustrates the procedural variables. There was a significant increase of the following in the cTnI positive group: chest pain ± ischaemic ECG changes during PCI (51.4% versus 13.9%, $P < 0.004$); numbers of stents used (42 versus 32, $P < 0.019$); and use of intravascular ultrasound during PCI (16% versus 2%, $P < 0.045$). There was no difference between the groups related to the total duration of PCI, the total numbers of balloon inflations per procedure, the number of lesions treated, balloon size, inflation time and pressure, or the antiplatelet regimes after PCI. The frequency and types of complications reported during and after PCI were significantly increased in the cTnI positive group. Out of the 37 patients in this group, 23 (62%) had complications compared to only 14 out of the 43 patients (32.5%) in the cTnI negative group ($P < 0.03$). These complications included one or a combination of the following: major dissection (27%, $P < 0.004$); transient vessel occlusion (19%, $P < 0.022$); bail out



Legend: cTnI = cardiac troponin I

Figure 2: Kaplan-Meier event-free survival analysis for the two groups of patients with cardiac troponin I (cTnI +) and without (cTnI -) elevations during angioplasty.

stents (19%, $P < 0.003$); AMI (8%, $P < 0.042$); side branch occlusion (SBO) (13.5%, P = NS); major technical failure of equipment during angioplasty (3%, P = NS); angina requiring re-catheterisation (13.5%, P = NS); and minor dissection (21.6%, P = NS).

Forty-two stents were used in this group compared to 32 stents in the cTnI negative group. The increased frequency of stents in this group was mostly to treat dissections (40.5% versus 17%, P = 0.05). Thirteen stents (31%) were used mostly on a bail-out basis to treat major dissection ± acute vessel closure. The use of stents for sub-optimal angioplasty results was slightly more in the cTnI negative group (49% versus 40.4%). Three patients developed AMI after PCI (1 Q wave and 2 non-Q wave AMI). The concentrations of cardiac markers in these patients were significantly elevated. H-FABP was the first marker to appear in significant concentrations after AMI. Peak concentrations of H-FABP, myoglobin, CK-MB mass and troponins occurred at 2 hours, 4 hours, 16–24 hours, and 16–24 hours respectively after angioplasty. The release patterns of cardiac markers were similar to the release patterns seen in Figure 1. H-FABP reached diagnostic concentrations for AMI 1–2 hours post-angioplasty. The diagnosis of AMI based on myoglobin, CK-MB mass, and troponins was established at 2–4, 4–16, and 4–16 hours respectively. Five patients had SBO during angioplasty. In 3 patients, this complication followed an extensive dissection. Out of the 5 patients, two developed AMI, two had considerable chest discomfort and ST segment depression ± T wave inversion, and in one patient the SBO was asymptomatic. Cardiac-TnI concentration was elevated in all patients. The mean cTnI increase in these three groups was 14.7 µg/L, 1.73 µg/L, and 0.18 µg/L respectively. Creatine kinase-MB mass, and myoglobin were increased in three patients, whereas H-FABP and CTnT were increased in two patients only. In the cTnI negative group, two patients had asymptomatic SBO, but there was no increase in cardiac markers in any of them. Forty-three patients had cTnI < 0.18 µg/L. Fourteen patients (32.5%) in this group developed complications during PCI; however, the frequency and severity of complications in this group were considerably lower than the cTnI positive group. These complications included one patient with major dissection, two patients with transient SBO, and one patient with transient vessel closure. The types of complications reported in the remaining 10 patients were minor dissections, coronary spasm, elastic recoil, and minor technical problems.

After discharge, clinical follow-up was possible in 79 out of 80 patients (98.75%). The mean follow-up period was 22.3 ± 1.7 months (range 20–26 months). The incidence of adverse clinical events is summarised in Table 3. Patients who had cTnI elevation post-PCI had a non-significant higher incidence of complications (angina pectoris, UA, and non-target vessel revascularisation). The total number of clinical events per group in the cTnI positive and cTnI negative group was 29/37 (78%) versus 21/43 (48%) respectively, P = NS. Three

patients who were included in the cTnI negative group had several adverse clinical events during follow-up (worsening of their angina, target and non-target vessel PCI, and CABG), despite uneventful PCI. Their cTnI concentration was between 0.08–0.11 µg/L. Surprisingly, cTnT was highly predictive of the need for CABG on long-term follow-up. Fifty per cent of patients with elevated cTnT after PCI were referred for CABG compared to only 4% of patients with normal cTnT after PCI ($P < 0.004$). There were no other statistical differences between the cTnT positive and negative groups when other cardiac events were compared between the two groups. The time-dependent effect of post-procedural cTnI elevation on late clinical outcome was assessed using the Kaplan-Meier survival analysis. There was a significant decrease in event-free survival with more recurrent angina, myocardial infarction, repeat PCI, and CABG in the group of patients who had cTnI elevations during angioplasty [Figure 2]. The mean event-free survival for the group with cTnI elevation and those without cTnI elevation was 16.92 months (standard error (SE) = 1.66, 95% confidence interval (CI) = 13.67–20.18, median = 23 months) versus 20.67 months (SE = 1.64, 95% CI = 17.46–23.88, median = 27 months) respectively ($P < 0.03$). Event-free survival was also decreased in cTnT and H-FABP positive groups. There were no event-free survival differences when CK-MB mass or myoglobin positive and negative groups were compared.

Discussion

The frequency of cTnI increases post-PCI in patients with complications was much higher than that seen with myoglobin, CK-MB mass, H-FABP, and cTnT. Cardiac-TnI was the most useful marker for the detection and quantification of PCI related complications. This reflects the superior sensitivity of cTnI for the detection of small releases of myocardial proteins after PCI. Heart-type-FABP was the earliest marker that could detect evolving AMI post-PCI within 1–2 hours and the concentration had returned to normal within 16–24 hours. H-FABP may be a potential early marker that can help select patients with chest pain, in the early post-PCI period, for early investigations to ascertain the diagnosis of AMI. There were different rises of concentrations of cTnI and other markers and different symptoms in the various subgroups of patients with SBO. These differences may be related to the size of the side branch vessel, the extent of collaterals, and the duration of the occlusion. The occurrence of asymptomatic SBO, and also the absence of the rise of concentration of cardiac markers following documented SBO has been reported by others.[10,13] Cardiac markers were also increased in the groups that had more stents and intravascular ultrasound investigations. Cardiac marker concentrations are elevated in some patients after PCI procedures involving stenting.[21] However, this increase indirectly reflects more complications, for example dissection in this group. It is not clear whether the use of intravascular ultrasound during PCI contributes to myocardial injury or merely reflects underlying complications.

Cardiac-TnI was increased in a small numbers of patients who had no complications reported during PCI. This may be due to: 1) the formation of small thrombi at the angioplasty site that may subsequently embolise to small distal arteries leading to small areas of focal necrosis; 2) the inability of contrast angiography to detect complications (indeed, intravascular ultrasound has been shown to be much more sensitive for the detection of coronary dissection after PCI compared with contrast angiography: 83% versus 27%;[8] 3) the variability of observers reporting complications and 4) mechanical trauma to the heart caused by guide wires manipulations within the coronary arteries. In our study, we found no apparent explanations for cTnI increases in 27% of patients, which was comparable to data published by Garbarz *et al*. who reported a 34% increase in cTnI concentrations in their study, which was not accounted for by complications during PCI.[22] The increases in cTnI, cTnT, CK-MB mass in the group with SBO was in agreement with Genser *et al*., who reported an increase in these markers in patients with SBO even when this complication was asymptomatic.[13]

The total frequency of cTnI rise (46.25%) in this study was slightly higher than that reported elsewhere in the literature. This could be explained by the use of cTnI sensitive assays with a relatively low cut-off concentration (≥ 0.18 µg/L) to indicate myocardial injury post-PCI. The frequency of CK-MB mass elevation in our study (11.25%) was lower than that reported previously (15–26%). This could be related to differences in assay methods used. Kugelmass *et al*. reported elevated CK-MB in 11.5% of patients following elective PCI, with no clinical sequels over

two years follow-up.[15] However, in a small subset with a greater elevation of CK-MB, there was a trend towards decreased late survival compared to patients without CK-MB elevation. They also reported common CK-MB elevation after coronary stenting.[15] An increased frequency of cardiac events on long-term follow-up (angina, PCI, CABG) was noticed in some patients who had very small increases of cTnI concentration (0.08–0.1 μg/L), which suggests that even small increases of cTnI may have a significant prognostic value and may reflect more diffuse or extensive CAD.

Long-term complications in patients with elevated cardiac markers post-PCI have been suggested by Abdelmeguid *et al*. who reported more frequent and more serious complications (e.g. death and AMI).[12] These differences could be related to several factors. First, the follow-up period in our study was relatively short compared to the study by Abdelmeguid (3–5 years, in some patients up to 8.5 years). Second, The use of stents was more frequent in the group of patients with elevated cardiac markers concentrations, which may alter the short-term risk of further progression to more serious complications.[23] Third, the use of newer and more potent antiplatelets regimes (clopidogrel, abciximab) was also high in our study. The clinical benefit of these antiplatelets compounds in reducing the progression to AMI and death in patients with myocardial injury is well-established.[24] Despite the fact that there were no statistically significant differences between the numbers of events, there was still a significant difference with respect to event-free survival between groups with and without elevations of these markers after angioplasty.

Increases in cTnT after PCI had been described previously.[17,21] Ravkilde *et al.* found moderate increases in CK-MB mass in 6 of 23 patients (26%) undergoing visually successful PCI, whereas only 3 (13%) showed cTnT elevation.[17] In this study, the percentage of positive cTnT results after PCI was only 7.5% using a third generation cTnT assay that was very sensitive (< 0.01 μg/L) and specific. Some of the previous studies used a lower cut-off concentrations e.g. ≥ 0.04 μg/L or ≥ 0.06 μg/L, to indicate the presence of myocardial injury post-PCI.[18,25] Increased cTnT ≥ 0.06 μg/L has also been found to be associated with increased risk of death and AMI (10.5%) compared to cTnT ≤ 0.06 μg/L.[25] Based on ROC curve analysis, a cut-off concentration of cTnT ≥ 0.06 μg/L was slightly more sensitive and equally specific to cTnT ≥ 0.1 μg/L for the detection of complications. Depending on whether the cut-off concentration used was ≥ 0.1 μg/L or ≥ 0.06 μg/L, the frequency of abnormal cTnT elevations was 7.5% and 12.5 % respectively. Despite the low sensitivity of cTnT, the specificity and positive predictive value for the detection of complications was very high. Event-free survival of patients with elevated cTnT concentrations was significantly lower than those without cTnT elevations after angioplasty. Cardiac-TnT was also associated with increased risk of CABG on long-term follow-up thus validating the prognostic significance of cTnT elevations post-PCI.

Measurements of cardiac markers post-PCI will be a useful adjunct to angioplasty and will help detect patients with subtle myocardial damage and may guide further management. Twelve patients (32%) with elevated cTnI in our study did not receive any form of antiplatelets (other than aspirin) during or after PCI. The cTnI concentrations range in these patients were 0.18–2.12 μg/L. Eight out of these 12 patients had worsening of their angina or further cardiac events during follow-up.

Conclusion

Heart-type-FABP measurements at 1 hour (or thereafter) post-PCI in patients with suspected complications may offer the best early chance of detecting evolving AMI. Cardiac-TnI has emerged as the most sensitive marker for the detection of major complications in patients undergoing PCI. It offers a reliable detection of myocardial damage that is sometime not obvious by visual assessment alone. The adjunctive measurements of cardiac markers post-PCI could help identify certain groups with elevated cardiac markers concentrations that might benefit from long-term treatment with newer antiplatelets therapy. Measurements of cTnI 16–24 hours post-PCI should be part of the work-up management of patients following elective PCI.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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