Correlation of Peri-Procedural Cardiac Enzyme Release with Atherosclerotic Plaque Burden using 3-D Fusion of Intravascular Ultrasound and Angiography

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Abstract. During the treatment of coronary atherosclerosis by percutaneous coronary interventions (PCI), cardiac enzymes indicating cell or muscle damage may be released and measured. Controversy exists regarding the importance of release of cardiac enzymes (i.e., the MB iso-enzyme of Creatine Kinase and Troponin) after coronary interventional procedures and the mechanism involved in this occurrence. While some have suggested that peri-procedural enzyme release or infarction may be a marker of atherosclerotic burden, others have shown its relationship to procedural complexity or plaque instability in unstable coronary syndromes. Using our previously developed and validated method for 3-D fusion of data from intravascular ultrasound (IVUS) and X-ray angiography, we investigated in 19 coronary vessel segments of 16 patients *in-vivo* whether peri-procedural cardiac enzyme release correlates with lesion or vessel atherosclerotic burden. Our results showed no evidence of a positive relationship, with consistent findings of a negative correlation between lesion and vessel atherosclerotic burden and the procedure-related release of cardiac enzymes. Except for a negative correlation between %-area stenosis and enzyme release ($p < 0.02$), none of the correlations was statistically significant. We concluded that cardiac enzyme release during complex PCI is not a marker of atherosclerotic burden, supporting previous concepts relating these indices to procedure complexity and unstable plaques.

1 Introduction

Cardiac enzymes specific to the heart, such as the MB iso-enzyme of Creatine Kinase (CK-MB) and Troponin I or T (TP), are commonly elevated in patients with coronary artery disease, and are the gold standard for measuring myocardial injury and myocardial infarction (heart attack). Elevations of these cardiac enzymes are also noted to occur during percutaneous coronary interventional procedures (PCI) in up to 30% of cases [1, 2]. Such enzyme elevations, when sufficiently high (more than three to five-fold higher than normal), may be associated with increased mortality [3]. These findings have led to

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considerable efforts to understand the pathophysiology of this peri-procedural cardiac enzyme elevation. Most efforts have focused on the relationship of these peri-procedural enzyme elevations to procedural complexity or to the unstable nature of the coronary plaque morphology. However, others have hypothesized that elevation of CK-MB after PCI is related to the atherosclerotic plaque burden, and may simply be a marker of the extent of the atherosclerotic process in a particular patient [2].

Intravascular ultrasound (IVUS) is well suited for assessing coronary plaque [4, 5]. In order to create a patient-specific geometrically correct 3-D model of a vessel, we have developed and validated a 3-D and 4-D fusion method, described in detail in [6, 7]. The methodology reported in this paper utilizes the 3-D model yielded by the fusion process to determine several morphological parameters, which are then correlated to the measured enzyme levels. While the vast majority of past data involving the relationship of cardiac enzyme release to PCI has been garnered from angiographic evaluations, IVUS imaging has been used in at least one prior study [2]. However, there have not been previous efforts to use IVUS for evaluating the possibility of a lesion-based explanation for peri-procedural cardiac enzyme release and PCI with actual measurements of atherosclerotic plaque and vessel volumes. We therefore performed a study to investigate whether or not a relationship exists between cardiac enzyme release during PCI procedures and morphological indices of atherosclerotic burden using 3-D IVUS/Angiography fusion.

2 Methods

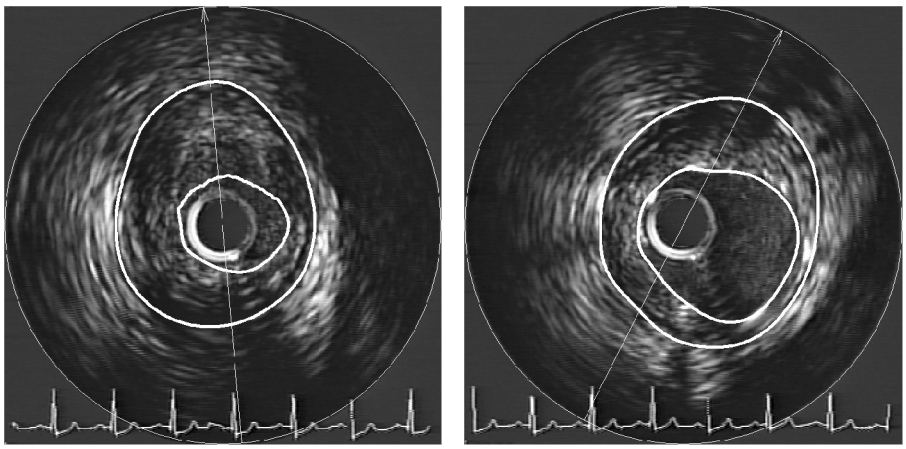
2.1 Acquisition and 3-D Fusion

Basis for the analysis was a 3-D model of the patient's coronary vessel under consideration. For this purpose, motorized-pullback data from IVUS were geometrically fused in 3-D space with a pair of single-plane X-ray angiographic images. The continuous pullback speed was 0.5 mm/s, pullback lengths of up to 10 cm were acquired. Angiographic imaging was performed prior to the start of the pullback with inclination angles of 60–120° between the two projections, showing both the IVUS catheter and the lumen of the vessel. While X-ray angiography images were directly available on DICOM media with 30 f/s, the IVUS data were recorded on S-VHS tape and digitized afterwards at 10–15 f/s speed. A General Electric Innova digital system was used for angiographic and a Boston Scientific ClearView console with 40 MHz Atlantis catheters was used for IVUS imaging.

For the following fusion step, the end-diastolic images were identified retrospectively, based on the ECG recorded in parallel with the image data. The fusion process was described in detail before [6, 7] and involves segmentation of both angiograpic and IVUS data followed by obtaining the correct location and orientation of each IVUS frame. This yields, at each IVUS frame location, a pair of 2-D contours in 3-D space indicating the interfaces between lumen and plaque as well as media and adventitia (Fig. 1). In order to compensate for overestimated cross-sectional areas due to an oblique orientation of the IVUS catheter within the vessel during imaging, all contours were perpendicularly resampled with respect to the vessel center line.

2.2 Patients and Plaque Types

Data from 19 stented vessel segments (6 in the left anterior descending artery, 5 in the left circumflex artery, and 8 in the right coronary artery) of 16 patients



(a) (b)

Fig. 1. Example for IVUS segmentation and final contouring of corresponding cross sections in (a) pre-interventional and (b) post-interventional pullbacks; contours mark the lumen-plaque and media-adventitia borders, arrows indicate corresponding spatial orientations after 3-D fusion.

(14 male, 2 female; mean age 63) were used in this study. One patient had one lesion each in two vessels, two patients each had two lesions stented in the same vessel. Prior written informed consent was provided by the patients and the study was approved by the internal review board of the University of Chicago. All patients were selected from stable patients undergoing clinically indicated cardiac catheterization and coronary intervention. They had either stable angina, positive stress testing or hospitalization for an acute coronary syndrome. No patient had evidence of ongoing acute myocardial infarction or ischemia, angiographic evidence of active thrombus or a thrombotic occlusion.

The patients were not specifically selected with respect to certain plaque types. Thus, the collected data contained vessel segments with both plaques that are echolucent in appearance and plaques showing attenuation in IVUS signal. Shadowing was accepted as long as the borders could be approximated by surrounding IVUS data. Total CK, CK-MB, and TP enzyme-release levels were recorded for each of the patients. For 14 of the 19 vessel segments, both pre- and post-interventional IVUS pullbacks were available for fusion; in the remaining 5 vessel segments, only pre-interventional pullbacks were available, thus not all parameters could be determined.

2.3 Stent Localization

Even though the pullback speed was identical in pre and post imaging, spacing of the retrospectively gated end-diastolic IVUS frames was usually different due to a varying heart rate. Also, the pullbacks usually differed in their distal start point, thus a landmark-based registration had to be performed between pre- and post-interventional pullbacks.

The pre- and post-interventional IVUS pullbacks were aligned with respect to one or more visible landmarks (branches or crossing vessels), and the stented segments identified in the post-interventional pullback. This allowed to determine the corresponding frames in the pre-interventional pullback as well as proximal and distal reference segments of up to 5 mm in an automated fashion

(Fig. 1). In those cases where no post-interventional pullback existed, stent locations were determined from the angiograms taken during PTCA and segment lengths matched with the known stent length. This procedure yielded 1,078 cross-sectional lumen-plaque/media-adventitia contour pairs in stented segments with pre/post-interventional IVUS imaging, 228 contour pairs from pre-interventional pullbacks only, and a total of 667 contour pairs in the reference segments.

2.4 Morphological and Statistical Analysis

For each pullback, the average, minimum, and maximum vessel, lumen, and plaque areas were calculated over the cross-sectional contour pairs. While these are commonly acknowledged parameters frequently used in conventional morphological analyses, it has to be emphasized that in each cross section, 72 lumen-plaque and 72 media-adventitia points were available for these area measurements. Also, the measurement plane was perpendicular to the vessel, not to the IVUS catheter, thus eliminating any errors introduced by an oblique imaging plane. These 2-D parameters were supplement by 3-D plaque volumes, measured over the respective vessel segments with roughly 0.5 mm spacing between adjacent cross sections, using the polytope method described in [8, 9]. Differences of these parameters between the pre- and post-interventional pullbacks were determined where applicable, thus yielding a maximum of 30 morphological parameters per stented segment.

All calculated parameters were linearly correlated with CK-MB and TP levels using regression analysis. For correlation coefficients $R > 0.3$ ($R^2 > 0.1$), we also determined the statistical significance of the slope of the regression line. For $p_{\text{slope}} < 0.05$, the correlation was considered significant.

2.5 Removal of Outliers

For 6 of the 19 vessel segments, the peri-procedural serum troponin T (TP) enzyme release was $< 0.03\,ng/mL$, thus reflecting a lack of myocardial injury during the procedure. Note that CK-MB levels may still be present since a rise in CK is not only caused by cardiac damage. In 2 stented segments, TP levels were extraordinarily high ($> 2\,ng/mL$). Therefore, we also determined the correlations in the remaining 11 segments separately to avoid noise from special cases.

3 Results

No parameter was highly correlated with enzyme levels, with correlations frequently better for CK-MB than TP levels. Correlations were in general better for averaged morphologic parameters than the minimum or maximum ones, likely due to the reduction of noise during averaging. Most correlations improved after the removal of outliers, as the example in Figure 2 demonstrates. Also, most correlations were negative, thus suggesting that higher enzyme release is associated with smaller morphological dimensions of plaque. The results are summarized in Figures 2 and 3 as well as in Tables 1 and 2.

The best and statistically significant (i.e., $p < 0.05$) correlations were seen in %-area stenosis with either CK-MB and TP release levels. Since %-area stenosis is a dimensionless parameter, and both CK-MB and TP levels are expressed in absolute numbers, we also determined the correlation between

Morphologic Parameter	n	CK-MB R slope	TP R slope
Plaque volume	19	$\Downarrow 0.227$, $p < 0.4$	$\Downarrow 0.226$, $p < 0.4$
%-area stenosis	19	$\Downarrow 0.483$, $p < 0.05$*	$\Downarrow 0.022$, $p \approx 0.9$
Vessel area	19	$\Downarrow 0.365$, $p < 0.15$	$\Downarrow 0.050$, $p \approx 0.8$
Lumen area	19	$\Uparrow 0.097$, $p \approx 0.7$	$\Uparrow 0.013$, $p \approx 0.9$
Lumen increase	14	$\Downarrow 0.479$, $p < 0.1$	$\Uparrow 0.195$, $p \approx 0.5$

*(*statistically significant; $\Uparrow$ = positive, $\Downarrow$ = negative correlation)*

Table 1. Correlations and significance of slope over all vessel segments.

Morphologic Parameter	n	CK-MB R slope	TP R slope
Plaque volume	11	$\Downarrow 0.490$, $p < 0.15$	$\Downarrow 0.422$, $p < 0.2$
%-area stenosis	11	$\Downarrow 0.749$, $p < 0.01$*	$\Downarrow 0.712$, $p < 0.02$*
Vessel area	11	$\Downarrow 0.431$, $p < 0.2$	$\Downarrow 0.320$, $p < 0.5$
Lumen area	11	$\Uparrow 0.394$, $p < 0.3$	$\Uparrow 0.404$, $p < 0.3$
Lumen increase	7	$\Downarrow 0.593$, $p < 0.2$	$\Downarrow 0.085$, $p \approx 0.9$

(vessel segments with TP release ≥ 0.03 and $< 2\,ng/mL$ only)

Table 2. Correlations and significance of slope after exclusion of outliers.

%-area stenosis and the CK-MB levels normalized over the total CK levels measured in the patients. Over all 19 segments, this resulted in an $R = 0.435$ with $p < 0.075$ and $R = 0.607$ with $p < 0.05$ for the 11 vessel segments with TP release $\geq$0.03 and $<2\,ng/mL$ only. While not statistically significant, similar correlation trends were seen with initial plaque volume and procedure-related lumen increase, both of which may be considered indicative of greater plaque burden. This is consistent with the pattern of a negative relationship between plaque burden and cardiac enzyme release during PCI.

4 Discussion and Conclusions

Increased CK-MB levels after PCI occurs in up to 11-35% of procedures. Recent work suggests that higher levels of cardiac enzyme release during PCI procedures are associated with higher mortality [3]. The pathophysiology underlying these events has been the subject of controversy with greater CK-MB release linked to procedure complexity, unstable plaque, and lesion type. Yet, it has also been suggested that cardiac enzyme release may simply be a marker of a more significant and severe atherosclerotic burden [2]. This distinction is important, as it may impact on decision making for PCI procedures. If mortality during PCI procedures is related to atherosclerotic burden, operators may determine that patients with more advanced disease may be less suitable for such procedures, instead offering therapies to patients with less advanced stages of atherosclerosis. If post PCI myocardial infarction and enzyme release (and perhaps late mortality) are instead a function of plaque instability or the presence of plaque rupture and an unstable coronary syndrome, then patients would not be considered "high risk" for PCI procedures solely on the basis of atherosclerotic burden.

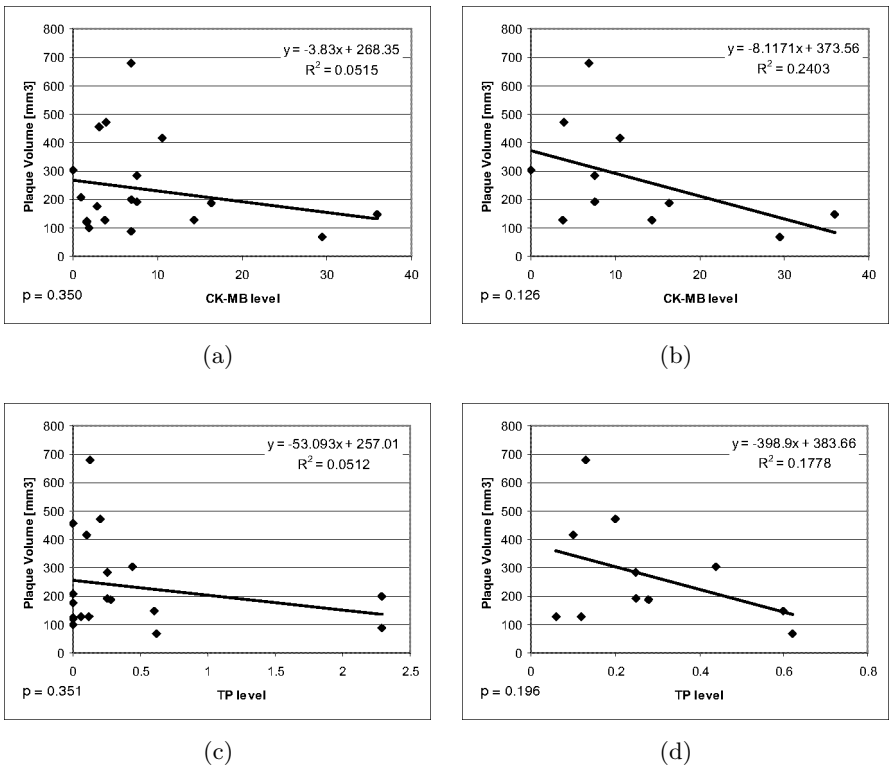


Fig. 2. Correlations between plaque volume $[mm^3]$ and (a,b) CK-MB release $[ng/mL]$, (c,d) TP release $[ng/mL]$; (a,c) over all vessel segments; (b,d) for those segments with TP release levels in the 0.03–2 ng/mL range, which clearly improves correlation and significance in this case.

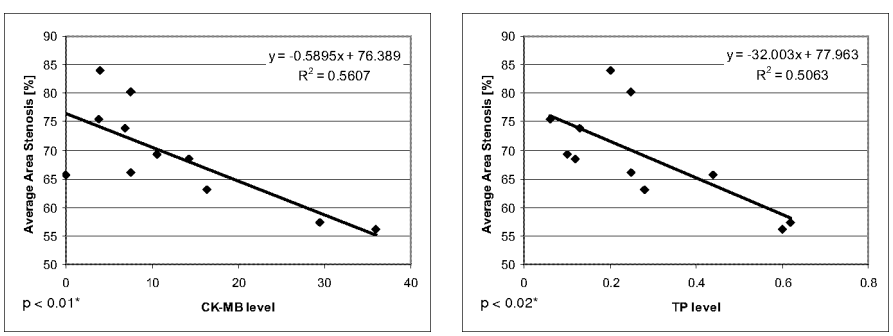


Fig. 3. Correlations between %-area stenosis and (a) CK-MB release $[ng/mL]$, (b) TP release $[ng/mL]$ for those segments with TP release in the 0.03–2 ng/mL range, showing the highest statistical significance. *(*statistically significant)*

In this study, we found no positive correlation between plaque burden or vessel size and the extent of enzyme release. Instead, there appears to be a convincing negative correlation between the extent of atherosclerosis and peri-procedural enzyme release. These findings result in a very different conclusion from a previous IVUS based study on over 2,000 patients [2] and are at odds with our initial hypothesis. Nonetheless, the results are consistent throughout our very meticulous data set. There may be several reasons why plaque volume in this patient population is negatively correlated with procedural cardiac enzyme release, a seemingly paradoxical finding. Today's understanding of acute coronary syndromes revolves around the concept of unstable or ruptured plaque, where mechanical lumen compromise by plaque does not need to be present, and where the instability of these incompletely obstructive lesions results in myocardial damage by promoting thrombosis. As such, patients with a stable atherosclerotic plaque burden phenotype may not suffer myocardial damage due to vessel remodeling and enlargement, despite an extensive plaque volume. We believe that this work supports these current concepts, where by extension, peri-procedural enzyme release and infarction does not reflect plaque burden, but plaque activity or instability or perhaps the complexity of a procedure itself.

Although the number of patients is small, the data is robust related to the amount of data evaluated per patient. While 19 lesions were evaluated, in all but one cases with multiple lesions per patient, multiple stents were used in treating one vessel rather than treating multiple vessels. Including multiple lesions of a single patient may introduce statistical issues as well as the problem of separating the enzyme level measurements over multiple interventions. Notwithstanding these limitations, our data is unique in regards to their ability to accurately and convincingly measure plaque burden and vessel dimensions throughout the treated lesion and vessel reference segment with a well-established 3-D angiographic/IVUS fusion system. The detailed analysis over 19 complete vessel segments with a total of 284,000 points available for measurements, along with a roughly 0.5 mm spacing between adjacent cross sections, provides a great deal of confidence that our methodology offers a level of investigation of vessel architecture and structure not previously possible. We envision a further extension of the set of 3-D parameters determined for this analysis, introducing new truely 3-D indices as recently done for our correlation study of plaque distribution with morphology and hemodynamics [10]

This analysis was not designed to evaluate the characteristics of plaque, given the fact that gray-scale IVUS was used. The results of this study, however, are provocative in suggesting that plaque characteristics, rather than simply overall plaque burden or volume, may be important in determining risk for periprocedural complications during PCI. As such, future work may confirm our findings in a larger patient population and will incorporate plaque characterization in patients who suffer procedural enzyme release, using newly available IVUS imaging techniques (Virtual Histology, [11]), which include radio-frequency analysis to characterize plaque types.

Acknowledgments

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