Can OCT change the therapeutic strategy in ACS due to plaque erosion?

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Abstract

The pathophysiology of acute coronary syndromes was thought to be coronary thrombosis over a plaque rupture. Autopsy studies revealed that not all cases were due to plaque rupture, even denuded endothelium or calcific nodule can beget a thrombus. Introduction of OCT made, in vivo recognition of lesion morphology clear. Plaque ruptures are most common and need primary angioplasty. Recent studies established plaque erosion is responsible for ACS in one third of the cases and majority of them present as Non ST elevation myocardial infarction and commonly found in young patients without major risk factors. Evidence from recent studies suggested that stenting can be deferred and they can be managed conservatively with good long term outcomes. More randomized trials are needed comparing plaque rupture and plaque erosion as regards conservative versus invasive management. If these studies substantiate the concept of conservative management, it will lead to a paradigm shift in their management.

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1. Introduction

Acute coronary syndromes (ACS) were thought to be due to coronary thrombosis secondary to underlying vulnerable plaque rupture (PR). This made thrombolytic therapy and primary percutaneous coronary interventions (PCI) as treatments of choice for their acute management to restore coronary circulation. Introduction of imaging particularly Optical Coherence Tomography (OCT) lead to in vivo recognition of underlying contributory mechanisms. Three types of plaque morphologies responsible for ACS have been recognized, PR being most common, followed by plaque erosion (PE) and calcific nodule (CN) being least common and responsible for 2–7% of acute coronary events.

2. Historical milestones

The initial reports were from autopsy studies of those who had sudden cardiac death (SCD) first reported by Van Der Wal in an autopsy series of 20 patients, 12 had PR and 8 PE. In another series of 50 patients of SCD, PE was noted in 44% and PR in 56%. Virmani et al. reported an autopsy series of 200 cases of SCD and observed PR to be responsible for ACS in only one third of their cases raising the suspicion of different mechanisms responsible for ACS. These

3. Definition of terms

PR - Fibrous cap discontinuity with communication between lumen and inner core of ulcerated large lipid rich plaque with cavity formation, with superimposed red thrombus (red blood cell rich) with significant lumen narrowing (Fig. 1).

PE - Luminal surface irregularities at the site of culprit lesion with or without superimposed thrombus, usually white thrombus (platelet rich) without large lipid core or calcification. The vascular structure is preserved with larger lumen (Fig. 2).

CN - Fibrous cap disruption over a calcified plaque, characterized by protruding calcium into the lumen or superficial calcium either at the proximal or distal ends of the lesion (Fig. 3).
Jia et al.\textsuperscript{1} from their observations described distinct features of PE. The eroded plaques were characterized by either absent or deeply seated necrotic core with intact fibrous cap with superimposed white thrombus attached to denuded endothelial layer. The pathology revealed thick fibrous cap, preserved media with disruption of superficial endothelial layer, lesser expansive remodeling, and lesser lipid accumulation and inflammatory cells like macrophages. C-reactive protein and total counts were not found elevated in cases of PE suggesting that inflammation was not likely cause for ACS in them.\textsuperscript{12} They postulated that thrombus removal by lytic therapy or thrombectomy may be sufficient to restore TIMI 3 flow in majority of these cases.

4. Prevalence of PE by OCT

Hayashi et al.\textsuperscript{13} were first to report their observations on in Vivo detection of PE by angioscopy in 39\% of their STEMI cases. Table 1 shows in vivo prevalence of PE in ACS by OCT observed in some of the studies which was found in 23\textendash 44\% of cases. CN was found to be least common and only in one study it was found to be high, 15\% of cases. It can be inferred that PE was found in 30\textendash 40\% of those who presented with ACS and had smaller infarcts in these reports.

5. Clinical presentation of PE

Table 2 shows NSTEMI was common presentation among PE and the occurrence highly varied from 60 to 84\% cases. In one large study\textsuperscript{19} of 318 patients, NSTEMI was found to be high, otherwise it was evident that approximately 2/3rds of PE cases presented as NSTEMI.

There are certain limitations in the detection of PE by OCT, most common being superimposed thrombus which can make accurate identification of lesion morphology difficult. If one looks carefully at the edges of the thrombus, there may be a possibility of identifying lesion morphology. It is understandable that mechanical thrombectomy and introduction of OCT catheter can add to the risk of distal embolization and modify plaque morphology. Parenteral antiplatelet therapy with GP 2b/3a inhibitors for 24\textendash 48 h may not alter the morphology of the underlying lesion. When patient's condition is unstable usually one may avoid imaging to make the procedure fast and simple. In patients with renal impairment contrast usage during OCT remains a limitation. OCT differentiation of calcium and lipid pool is more challenging as both result in low attenuation signals and its detection needs experience and skill.\textsuperscript{23} Due to limited ranging depth of OCT (5\textendash 6 mm) imaging lesions in left main stem, ectatic coronaries and vein grafts was reported to be difficult.\textsuperscript{24} PE is a diagnosis of exclusion by OCT and was not done in all cases of ACS, so the published studies does not represent overall ACS population. Valid histological confirmation may not be possible in all cases and in Octovia study only in 69\% of 140 lesions, OCT characterization could be possible.\textsuperscript{16}
6. Management strategies in PE

The management will depend upon the patient’s clinical condition. Current guidelines recommended early PCI with stenting of the culprit lesion. ACS due to PR were reported to have larger infarcts, poorer LV functions and higher chances of no reflow phenomena with PCI. The reported studies revealed variable outcomes with PCI in cases of PE. In one large series of 318 cases PE was found to have better long term prognosis with PCI compared to PR during 18 months follow up. Niccoli et al. reported lesser MACEs (major adverse cardiovascular events) in cases of PE (14%) compared to those with PR (39%) during 3 yrs follow up. When there was evidence of less than TIMI 3 flow it is reasonable to stent these vessels but majority of NSTEMI due to PE were found to present with TIMI 3 flow in whom there was an option of deferred stenting. Higuma reported lesser microvascular damage and myocardial necrosis in PE after PCI. Study by Saia et al. did not find any difference between PE and PR after PCI. Contrary to these studies Hu et al. showed poor vascular healing following DES in cases of PE compared to those with PR during 6 months follow up. Prati et al. reported an observational study of 31 patients of PE who have undergone thrombectomy and remained asymptomatic during 2 yrs follow up. Forty percent of them were managed on dual antiplatelet therapy (DAPT) alone whereas rest 60% needed PCI in addition to DAPT. All of them remained asymptomatic during follow up suggesting an option of deferred stenting in selected cases of ACS due to PE.

Erosion Study was the first prospective study of STEMI where 25% of their cases were found to be due to PE. When OCT revealed PE with less than 70% luminal narrowing of the culprit vessel with TIMI 3 flow, stenting was avoided in them. At 1 month, follow up OCT revealed greater than 50% reduction in thrombus volume and all of them except 2 cases remained asymptomatic, this became a landmark proof of concept study. Follow up of Erosion study population revealed that Tirofiban infusion provided additional benefit. Thrombus resolution with Tirofiban in conservatively managed patients with PE was also reported by Sugayama et al. The TOTAL study substantiated that there was no benefit of mechanical thrombus aspiration in these cases and it may even add to the risk of distal embolizations and stokes. Avoiding stenting in cases of PE can reduce the risk of stent thrombosis, restenosis, long term use of DAPT. Souteyrand et al. reported that in the absence of PR with ≤70% narrowing of the culprit vessel, stenting was avoided in their OCT guided prospective study. Two step treatment strategy was followed by them in cases of PE in 46 patients compared to 136 with stenting in whom delayed coronary angiograms and OCT were done after a mean period of 6 days. Twenty three patients were benefited from this approach of systematic delayed OCT over a mean follow up of 171 days in whom mean luminal area was found increased during follow up. At 1 year only 2 patients who presented with angina needed stenting.

7. Clinical predictors of PE

Yonetsuz et al. in their retrospective registry data suggested a logistic regression model showed that 5 parameters can clinically predict PE age <68 years, anterior ischemia, normal renal functions, Hb > 15 gms % and absence of diabetes and demonstrated the probability of underlying PE to be 73%. Pratida et al. suggested that in young individuals with NSTEMI without major risk factors one can clinically predict PE and plan OCT which is key to the definitive diagnosis and this subset of patients can be managed conservatively with antithrombotic therapy. Jinnan Dai et al. in a large prospective study of 209 cases of ACS who have undergone OCT observed PE to be more common in premenopausal women, current smokers and those with fewer risk factors compared with those with PR. In addition they reported PEs were common at bifurcation points. In their multivariate analysis, reported that 5 parameters can clinically predict PE age <68 years, anterior ischemia, normal renal functions, Hb > 15 gms % and absence of diabetes and demonstrated the probability of underlying PE to be 73%. Pratida et al. suggested that in young individuals with NSTEMI without major risk factors one can clinically predict PE and plan OCT which is key to the definitive diagnosis and this subset of patients can be managed conservatively with antithrombotic therapy. Jinnan Dai et al. in a large prospective study of 209 cases of ACS who have undergone OCT observed PE to be more common in premenopausal women, current smokers and those with fewer risk factors compared with those with PR. In addition they reported PEs were common at bifurcation points. In their multivariate analysis, reported that when patients of <50 Yrs age with current smoking, absence of major risk factors, absence of multi vessel involvement, large vessel size, less severe lesions, particularly near bifurcation sites one should suspect PE and OCT must be planned to confirm the diagnosis. DAPT without stenting showed 92% of MACE free survival at 1 year in their study. The major limitation of their study was that...
they included only STEMI cases. It should be kept in mind that in the same patient there can be even distribution of thin cap fibroatheromas and stable thick fibrous capped plaques. Araki Seda et al. demonstrated by OCT thin cap fibroatheromas in proximal segments of coronaries particularly in left anterior descending artery in patients of ACS and thick capped fibrous plaques evenly distributed along entire length of coronaries suggesting that both PR and PE can coexist in the same patient at different sites. In some of the reported studies sample sizes were small, there was selection bias and randomization was lacking in few. There was no long term data available regarding stent thrombosis, restenosis, clinical outcomes with PCI in cases of PE comparing with those of PR. Hence there is a need for further randomized controlled trials with OCT in cases of ACS comparing PE with PR.

8. Ongoing registry

Massachusetts general hospital retrospective OCT registry of 141 patients of ACS showed 56% PR and rest PE. Of the ACS due to PR, 97.5% have undergone stenting whereas only 79% were stented among those due to PE. Post intervention OCT showed higher incidence of malappositions, thrombus, distal embolizations and no-reflow among PR. One year MACES were comparable between both the groups but none of PE cases in whom stenting was deferred had MACE. Interim observations revealed that post stenting unfavorable outcomes were frequent with PR indicating that one can defer stenting in those with PE. This observational 5 year follow-up study is expected to be completed by May 2021 and the final results will give some more directions regarding tailored management of ACS due to PE.

9. Future directions

Development of biomarkers to differentiate PE from PR may be a step forward. Increased levels of systemic myeloperoxidase levels were observed in patients of ACS due to PE compared to PR. In postmortem coronary specimens, luminal thrombi superimposed on PE were shown to have higher density of myeloperoxidase positive cells compared to those thrombi over PR. Whether lipid lowering (statin) therapy has got plaque stabilizing effect both on PR and PE needs further studies. As diabetic population is more prone for ACS there is a need for further studies comparing PR and PE as regards prevalence, presentation and management strategies in them.

10. Conclusions

PE can be detected in one third cases of ACS and commonly they present as NSTEMI. PE is a diagnosis of exclusion and OCT is essential for the definitive diagnosis. They can be managed conservatively with DAPT and GP 2b/3a inhibitors in selected cases and stenting can be deferred. In young patients of ACS with NSTEMI without major risk factors one can predict PE and OCT must be planned while performing CAG to confirm the diagnosis. “Seek and ye shall find (Bible)”. If one looks for plaque erosion, one can find by OCT in 1/3rd cases of ACS, but this needs high index of suspicion. There is a need for large scale randomized trials in ACS with PE and PR comparing conservative with conventional invasive management. Routine use of OCT in all cases has not been recommended during primary PCI but this may be incorporated in the guidelines in future if more data is made available. This concept will lead to a major paradigm shift in the diagnosis and management of ACS due to PE.

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