Coronary Angiography (CAG) and Fractional Flow Reserve (FFR) in Asymptomatic Patients with Prior Acute ST- Segment Elevation Myocardial Infarction (STEMI), Who Were Successfully Treated with Fibrinolysis, and Had Normal Post Discharge Exercise Stress Testing

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Background: *Fibrinolysis is still used as the main method of reperfusion therapy in many hospitals. However, management of asymptomatic, post-acute ST-segment elevation myocardial infarction (STEMI) patients who were successfully reperfused with fibrinolysis, is still controversial.*

Objective: *To study the results of coronary angiography (CAG) and fractional flow reserve (FFR) in asymptomatic, post-acute STEMI patients who were successfully treated with fibrinolysis, and had normal post discharge exercise stress testing.*

Material and Method: *The authors performed CAG on all post-acute STEMI patients, who met all the following inclusion criteria, 1) history of successful fibrinolysis at referral hospital, 2) no history of recurrent or residual ischemic chest pain, 3) no clinical heart failure or significant arrhythmia, and 4) normal post-discharge EST. FFR was done if the patient had an infarct-related artery (IRA) diameter stenosis of 40% or more.*

Results: *Thirteen patients met all the inclusion criteria during the six months study period. All of them had residual severe stenosis in the IRA by CAG. The average degree of residual stenosis was 84.6±8.5% (range 70% to 95%). FFR was performed on all 13 patients and showed significant functional IRA stenosis in 11 patients with the average FFR value of 0.64±0.18 (range 0.22 to 0.75). All the patients who had significant FFR at the IRA received percutaneous coronary intervention (PCI). One patient with ulcerated plaque, but non-significant FFR, also received PCI.*

Conclusion: *Most asymptomatic, post-acute STEMI patients who were successfully reperfused with fibrinolysis and had normal post-discharge EST, still had residual severe stenosis of the IRA and significant FFR. Skipping the EST and directing the patient to CAG with FFR-guided PCI should be considered.*

Keywords: *Post STEMI patient, Fibrinolysis, FFR-guided PCI*

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Primary percutaneous coronary intervention (PCI) is the recommended reperfusion therapy over fibrinolysis in patients with acute ST-segment elevation myocardial infarction (STEMI) if performed by an experienced team within 120 minutes of first medical contact[1]. However, primary PCI has several limitations, and fibrinolysis is still used on many patients. Recent clinical trials, as well as guidelines, recommend immediate transference of all high-risk acute STEMI patients after fibrinolysis to a PCI-capable center and coronary angiography (CAG) with a view to revascularization of the infarct-related artery (IRA) if indicated, even after successful fibrinolysis therapy. The optimal timing of CAG, after successful fibrinolysis, is between 3 and 24 hours[1-4].

Unfortunately, many acute STEMI patients, with successful fibrinolysis, cannot have CAG done within the first 24 hours. Risk stratification by non-invasive testing for example exercise stress test (EST), is recommended for this group of patients[2]. Only patients with abnormal non-invasive tests should undergo CAG and revascularization if indicated. Patients with normal non-invasive tests, called low-risk groups, do not need to have CAG done and conservative medical therapy is recommended. However, this recommendation is still controversial. Previous study demonstrated poor correlation between pre-discharge

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non-invasive testing and CAG in this group of patients. Thus, the study argued for a simpler strategy of routine CAG, even after low-risk STEMI[5].

On the other hand, studies also demonstrated poor concordance between CAG, or anatomical stenosis along with fractional flow reserve (FFR). This means an anatomical significant lesion in post STEMI patients does not translate to functional significant FFR (anatomical-functional mismatch). Therefore, the simpler strategy of routine CAG (anatomical risk stratification) does not offer any clinical benefits if PCI to the culprit lesion with anatomical significant stenosis by CAG, but non-significant FFR. Currently, FFR is the gold standard for inducible ischemia and correlation with prognosis[6,7].

FFR, or functional significant stenosis of the IRA, has never been reported in this STEMI subgroup. The aim of the present study was to report the results of CAG and FFR in STEMI patient who were successfully treated with fibrinolysis without clinical or EST evidence of residual myocardial ischemia.

Material and Method

Between October 1, 2014 and March 31, 2015, the authors performed CAG on all patients who were referred to our hospital and met all the following inclusion criteria 1) history of acute STEMI successfully reperfused with fibrinolysis as indicated by resolution of ST-segment of at least 50%, with improvement of chest pain being documented by attending physician at the referral hospital, 2) no history of recurrent or, residual ischemic chest pain after fibrinolysis up until the time of CAG, 3) no high-risk characteristics for example clinical heart failure or cardiac arrhythmia, and 4) normal post discharge EST. The authors proceeded to FFR if the patient had an IRA diameter stenosis of 40% or more. Informed consent for the procedures was obtained from each patient.

Procedures

EST: maximum, symptom-limited, treadmill exercise electrocardiography (ECG) testing was performed at three to six weeks after STEMI, in patients without any ischemic symptoms to determine risk and prognosis as well as evidence of residual myocardial ischemia. A conclusive negative exercise response is defined as no significant ST-segment depression at heart rate of 85% or greater of the age-predicted maximum without exercise induced ischemic chest pain, significant arrhythmia and abnormal blood pressure responding. Patients who had abnormal EST or cannot perform EST were excluded from the study.

CAG was done either via the femoral or radial artery. The degree of coronary artery stenosis was assessed by visual estimation. Patients who met all the above inclusion criteria with coronary artery stenosis, either culprit or non-culprit vessel, of 40% or more proceeded to FFR within the same session. To optimize the vessel diameter and exclusion of coronary spasm, an intracoronary (IC) bolus injection of 100 to 200 microgram nitroglycerine was given to all patients with significant coronary artery stenosis.

The FFR was measured by using a 6 French guiding catheter. A 0.014 inch Pressure Wire (St. Jude Medical Systems, Uppsala, Sweden) was carefully calibrated and then passed through the lesion. Maximum hyperemia was induced by IC injection of 100 microgram bolus dose of adenosine ahead of FFR measurement. The maximum bolus dose of IC adenosine was 200 micrograms, if tolerated. An FFR value of 0.80 or less identified ischemia-producing coronary stenosis (functional significant stenosis) and mandated PCI even though there were no symptoms. Curve equalization as systematical was checked at the end of the procedure, on withdrawal of the FFR wire, with exclusion if a deviation of 0.02 or more.

PCI with, or without IVUS guided was performed using standard techniques and with drug-eluting stents. All patients received 81 mg/day of aspirin, 75 mg/day of clopidogrel after STEMI and 70 to 100 units/kilogram body weight, IV bolus dose of unfractionated heparin in catheterized laboratory.

Statistic

Data were analyzed and expressed as mean value and SD.

Results

During the study period of six months, 791 patients with acute or chronic coronary artery disease underwent CAG with a view to revascularization. Of the 791 patients, 13 met all inclusion criteria. Overall, patients had good functional capacity with an average of 9.9 METs by treadmill EST (Table 1). The median time since acute STEMI until CAG and FFR was seven weeks (range 4 to 10 weeks). All 13 patients had severe IRA stenosis by CAG. The culprit vessel was the left anterior descending artery (LAD) in 8 out of 13 patients. The average degree of diameter stenosis, and lesion length was 84.6±8.5% (range 70% to 95%), and 28.±16.8 mm (range 10 to 74 mm) consecutively.

Table 1. Baseline characteristics, coronary angiography results and fractional flow reserve (FFR)

Case number	Age	Sex	Infarct related artery (IRA)	Functional capacity (METs)	Max HR	CAG% stenosis at culprit lesion	Lesion length (mm)	Presence of non-culprit vessel stenosis	FFR of the culprit lesion	PCI
1	59	M	RCA	10.0	136	80	12	No	0.81	No
2	41	F	LAD	10.0	160	80	30	No	0.68	Yes
3	59	M	LAD	7.0	146	80	40	No	0.75	Yes
4	51	M	LCX	10.0	144	90	30	Yes	0.68	Yes
5	43	M	LAD	12.8	150	95	20	No	0.22	Yes
6	38	M	LAD	10.0	169	70	20	Yes	0.84	Yes*
7	47	M	RCA	10.0	148	95	10	Yes	0.37	Yes
8	45	M	LAD	12.8	176	70	26	No	0.73	Yes
9	52	M	RCA	10.0	146	90	18	Yes	0.72	Yes
10	50	M	LAD	12.8	148	80	20	No	0.76	Yes
11	50	M	RCA	7.0	152	90	24	Yes	0.72	Yes
12	73	M	LAD	7.0	127	90	44	No	0.55	Yes
13	55	M	LAD	10.0	132	90	74	No	0.49	Yes
Mean ± SD	51.0±9.2			9.9±2.0		84.6±8.5	28.0±16.8		0.64±0.18	

M = male; F = female; Max HR = maximum heart rate; CAG = coronary angiography; PCI = percutaneous coronary intervention; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery
* PCI was done due to ulcerated plaque

Five out of the 13 patients also had angiographical significant stenosis in non-culprit vessels. Eleven out of 13 patients had FFR value of less than 0.80, indicating functional significant stenosis. The average FFR of the culprit vessel was 0.64±0.18 (range 0.22 to 0.75). Two out of 13 patients had FFR value of more than 0.80, despite severe stenosis by CAG. IRA-PCI was conducted in every patient who had significant FFR. However, a patient with FFR value of 0.84 underwent PCI, because of unstable plaque morphology (ulcerated plaque). There was no procedural related complication.

Discussion

Current guidelines recommended immediate transfer of the high-risk acute STEMI patient treated with fibrinolysis to PCI-capable center for early CAG within the first 24 hours even though successful fibrinolysis. In all trials, fibrin specific agents were used for fibrinolysis[3,4,8]. Many patients still received Streptokinase, and could not have CAG done within the first 24 hours. Patients are usually transferred to a PCI-capable center or tertiary hospital for elective evaluation later.

Management of STEMI patients, who are successfully reperfused with fibrinolysis without recurrent ischemic symptoms is controversial. The previous guideline recommended risk stratification by non-invasive tests for this group of patients. It is also recommended that the use of conservative medical treatment is applied if a patient is classified as low-risk, or has normal non-invasive tests. This is because the most widely available and the cheapest exercise ECG testing or EST is usually used for this purpose.

However, many years ago, Jaffe et al reported the discordance between non-invasive tests, namely EST and myocardial perfusion scintigraphy, and CAG in "low-risk" STEMI patients, who were successfully treated with fibrinolysis. The study reported up to 56% of patients still had residual, severe (≥70%) IRA stenosis and 16% had multi-vessel disease[5]. The study suggested routine CAG, so called "anatomical risk stratification", in most patients after low-risk STEMI.

In the past decade, FFR was widely evaluated, and accepted as the gold standard for diagnostic of a significant ischemia-producing lesion. Studies also showed discordance between FFR and degree of coronary artery stenosis even when estimated by experienced cardiologists[9,10]. That means significant anatomical stenosis may not translate to significant FFR, especially in cases of prior MI. In other words, the culprit lesion, which is classified as severe stenosis by CAG, may not require PCI.

The present study aimed to evaluate anatomy as well as functional significant lesions in post STEMI patients. The present study revealed that all STEMI patients who were successfully treated with fibrinolysis with no recurrent chest pain and normal EST still have severe IRA stenosis on CAG. The incidence of residual

severe IRA stenosis may be too high. This is probably due to the limited number of cases, or by chance. Another finding was that FFR was significant in most of our cases. This means normal EST in this group of patients is not sensitive enough to detect residual ischemic burden, nor can it exclude functional significant IRA stenosis. Moreover, three patients who had significant FFR in the LAD territory, had normal EST despite reaching high workload of exercise at 12.8 METs. Therefore, normal EST at high workload is still unreliable to detect myocardial ischemia, even a large ischemic area such as the LAD territory. Two out of 13 patients had non-significant FFR despite severe IRA stenosis. Therefore, the combination of both CAG and FFR is important for patients' evaluation.

Although EST is widely available, the limitation to detect myocardial ischemia, as indicated by significant FFR, may mislead our decision making in management of this STEMI subgroup. An undetected residual IRA severe stenosis may silently progress to chronic total occlusion, which may lead to troubles in the treatment within the near future. All patients in the present study must receive conservative medical treatment if the treatment option relied solely on EST results.

The present study suggests skipping EST for risk stratification in post STEMI patients, who were successfully treated with fibrinolysis. An asymptomatic post STEMI patients, who were successfully treated with fibrinolysis should be directed to CAG, for anatomical risk stratification and FFR if anatomical significant stenosis. A simple strategy of routine CAG is recommended.

Limitation

The major limitation of the present study was the small number of patients. Therefore, the incidence of significant stenosis of IRA along with significant FFR in the present study did not represent the true incidence for the whole patient population. Even though the sample size was small in the present study, the functional significant IRA stenosis was found in most patients.

What is already known on this topic?

Previous study demonstrated high incidence of residual, severe (≥70%) IRA stenosis in post-acute STEMI patients, who were successfully reperfused with fibrinolysis, and had normal EST and myocardial perfusion scintigraphy.

What this study adds?

The present study showed high incidence of both anatomical and functional significant IRA stenosis (significant FFR) despite normal EST. Skipping the EST whilst directing the patients to CAG with FFR-guided PCI should be considered.

Potential conflicts of interest

None.

References

1. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569-619.
2. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the management of patients with acute myocardial infarction). J Am Coll Cardiol 2004; 44: E1-E211.
3. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Briales J, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. Lancet 2004; 364: 1045-53.
4. Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med 2009; 360: 2705-18.
5. Jaffe R, Halon DA, Ben Haim S, Shiran A, Gips S, Karkabi B, et al. Reevaluation of routine invasive strategy versus non-invasive testing following uncomplicated ST-elevation myocardial infarction. Cardiology 2006; 105: 240-5.
6. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJ, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996; 334: 1703-8.
7. Pijls NH. Optimum guidance of complex PCI by coronary pressure measurement. Heart 2004; 90: 1085-93.
8. Scheller B, Hennen B, Hammer B, Walle J, Hofer C, Hilpert V, et al. Beneficial effects of immediate

stenting after thrombolysis in acute myocardial infarction. J Am Coll Cardiol 2003; 42: 634-41.
9. Brueren BR, ten Berg JM, Suttorp MJ, Bal ET, Ernst JM, Mast EG, et al. How good are experienced cardiologists at predicting the hemodynamic severity of coronary stenoses when taking fractional flow reserve as the gold standard. Int J Cardiovasc Imaging 2002; 18: 73-6.
10. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010; 55: 2816-21.

ผลการฉีดสีตรวจหลอดเลือดหัวใจ และ fractional flow reserve ในผู้ป่วยที่เคยเป็นโรคหลอดเลือดหัวใจอุดตันเฉียบพลันชนิดที่มีการยกของคลื่นไฟฟ้าหัวใจส่วน ST และได้รับการรักษาด้วยยาละลายลิ่มเลือดเป็นผลสำเร็จและผลการทดสอบสมรรถภาพหัวใจด้วยการเดินสายพานได้ผลปกติ

นพดล ชำนาญผล, สิริชัย ชีวธนากรณ์กุล, ศรัณยู สุวรรณอักษร

ภูมิหลัง: *ยาละลายลิ่มเลือดยังใช้เป็นการรักษาหลัก สำหรับผู้ป่วยโรคหลอดเลือดหัวใจอุดตันเฉียบพลันชนิดที่มีการยกของคลื่นไฟฟ้าหัวใจส่วน ST ในหลายโรงพยาบาล อย่างไรก็ตามการรักษาหลังจากสามารถเปิดการไหลเวียนเลือดด้วยยาได้ผลดีแล้ว ยังไม่มีแนวทางที่ชัดเจน*

วัตถุประสงค์: *เพื่อศึกษาผลการฉีดสีหลอดเลือดหัวใจ และการตรวจ fractional flow reserve (FFR) ในผู้ป่วยที่เคยเป็นโรคหลอดเลือดหัวใจอุดตันเฉียบพลันชนิดที่มีการยกของคลื่นไฟฟ้าหัวใจส่วน ST ที่ได้รับการรักษาด้วยยาละลายลิ่มเลือดเป็นผลสำเร็จแล้ว*

วัสดุและวิธีการ: *ผู้นิพนธ์ทำการฉีดสีหลอดเลือดหัวใจให้กับผู้ป่วยที่เคยเป็นโรคหลอดเลือดหัวใจอุดตันเฉียบพลันทุกรายที่เข้ากับเกณฑ์ต่อไปนี้ครบทุกข้อ 1) มีประวัติได้รับยาละลายลิ่มเลือดและยาสามารถเปิดการไหลเวียนเลือดได้ผลสำเร็จ 2) ไม่มีอาการเจ็บแน่นหน้าอกหลงเหลืออยู่หรือมีอาการเจ็บแน่นหน้าอกซ้ำ 3) ไม่มีอาการหัวใจวายหรือหัวใจเต้นผิดจังหวะชนิดรุนแรง และ 4) การทดสอบสมรรถภาพหัวใจด้วยการเดินสายพานได้ผลเป็นปกติ หากการฉีดสีตรวจพบว่ามีหลอดเลือดหัวใจตีบมากกว่าหรือเท่ากับร้อยละ 40 ผู้ป่วยจะได้รับการตรวจ FFR ต่อไป*

ผลการศึกษา: *ในระยะเวลา 6 เดือน ผู้ป่วย 13 ราย เข้าเกณฑ์ข้างต้น และผลการฉีดสีตรวจหลอดเลือดหัวใจ พบว่าผู้ป่วยทุกรายยังคงมีหลอดเลือดหัวใจตีบรุนแรง เฉลี่ยร้อยละ 84.6±8.5 ของเส้นผ่าศูนย์กลางหลอดเลือด ผลการตรวจ FFR ในผู้ป่วยทั้ง 13 ราย พบว่าให้ผลผิดปกติ 11 ราย ค่าเฉลี่ยของ FFR เท่ากับ 0.64±0.18 ผู้ป่วยทุกรายที่ค่า FFR ผิดปกติ และผู้ป่วย 1 ราย ที่ FFR ปกติ แต่มี ulcerated plaque ได้รับการทำบอลลูนขยายและใส่ขดลวดค้ำยันหลอดเลือดหัวใจ*

สรุป: *ผู้ป่วยที่เคยเป็นโรคหลอดเลือดหัวใจอุดตันเฉียบพลันชนิดที่มีการยกของคลื่นไฟฟ้าหัวใจส่วน ST แม้ว่าได้รับการรักษาด้วยยาละลายลิ่มเลือดได้ผลดี ไม่มีอาการหลงเหลืออยู่ และผลการตรวจทดสอบสมรรถภาพหัวใจด้วยการเดินสายพานเป็นปกติ เมื่อตรวจด้วยการฉีดสีหลอดเลือดหัวใจยังคงมีหลอดเลือดหัวใจตีบมาก และผลการตรวจ FFR ผิดปกติเป็นส่วนใหญ่ ดังนั้นเมื่อให้การดูแลรักษาผู้ป่วยกลุ่มนี้ ควรทำการฉีดสีตรวจหลอดเลือดหัวใจและตรวจ FFR ร่วมด้วย โดยไม่มีความจำเป็นต้องทดสอบสมรรถภาพหัวใจด้วยการเดินสายพานก่อน*