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FRACTIONAL FLOW RESERVE IN PATIENTS WITH INTERMEDIATE VALUES OF DUKE TREADMILL SCORE AND BORDERLINE CORONARY LESIONS

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Abstract - Despite the wide usage of exercise ECG tests and Duke Treadmill Score (DTS) in clinical practice, no comparison between this scoring system and Fractional Flow Reserve (FFR) has yet been made, particularly in cases of angiographically verified borderline lesions. Thirty patients with single coronary lesions and angiographically assessed borderline stenosis (between 30-70%) and previously calculated intermediate values of DTS between -10 to +4 were examined using FFR. Adequate specificity and sensitivity (0.769 and 0.556, respectively) were in a more narrow range of -0.5 to -10. Sex and age did not have an influence on the DTS values. There was a correlation between the values of FFR and age (r=0.395, p=0.031) and between angiographic assessment of stenosis and quantitative coronary angiography (QCA) (r=0.648, p<0.0001). In the study population, a decision on revascularization could not be based solely on angiographic or QCA assessment of the artery or on the values of DTS.

Key words: FFR; exercise ECG test; DTS; intermediate coronary stenosis; QCA

Abbreviations: FFR – Fractional Flow Reserve, QCA – Quantitative Coronary Angiography, DTS – Duke Treadmill Score, DS – Diameter of Stenosis, LCA – Left Coronary Artery, LAD – Left Anterior Descending Artery, LCX – Left Circumflex Artery, RCA – Right Coronary Artery

INTRODUCTION

One of the key problems in deciding on the need for revascularization of the myocardium is the exact determination of hemodynamically significant (ischemic) lesions. In common clinical practice, the decision to perform percutaneous coronary intervention (PCI) is based on a subjective angiographic and clinical assessment of the target lesion, resulting in great inter- and intra-observer variations (De Rouen et al., 1977, Beauman et al., 1990, Meier et al., 1983). Pathohistological examinations also showed large discrepancies compared to angiographic studies (Grondin et al., 1974, Arnett et al., 1979, Isner et al., 1981).

The limitations of angiography are amplified in borderline lesions (lesions between 30-70% diameter stenosis, DS) and the decision to perform revascularization is based on non-invasive testing. Most common of all is exercise ECG stress testing (EET), which is often inconclusive or borderline in such cases.

Since its introduction more than 60 years ago (Master et al., 1944), exercise stress testing has become the most used test for the detection of coronary disease. Despite wide usage, precision in detection of significant coronary lesions is doubtful. Most recent guidelines show a test sensitivity of 45-92% and specificity 17-92%, based on numerous studies and meta-analyses (Gibbons et al., 1997). Diagnostic accuracy has been somewhat improved by using various prognostic scoring systems (Berman et al., 1978; Hollenberg et al., 1985; Detrano et al., 1992; Morise et al., 1992; Do et al., 1997).

Duke Treadmill Score

One of the most commonly used prognostic scores in clinical practice is the Duke Treadmill Score (Mark et al., 1987), calculated by the formula:

DTS=T-(5xSTd)-(4xA),

where T – time in minutes of exercise, STd – ST depression in mm, A – anginal pain graded: 0 – no chest pain, 1 – non limiting chest pain, 2 – test limiting chest pain. Values of DTS < -11 are indicative of high-risk patients (annual cardiovascular mortality 5-7%), and values > 5 are considered low risk (annual mortality 0.25-0.5%). Patients with a score between cut-off values (-10 to +4) are classified as intermediary risk (annual mortality 1.25-2%).

This composite index links electrocardiographic and clinical parameters. It is easy to perform and it provides additional prognostic information compared to the standard stress ECG test.

Angiographic studies have compared its correlation to echocardiographic Doppler based CFR (coronary flow reserve) in patients with microvascular angina (Ho-Joong et al., 2005), stress echocardiography (Peteiro et al., 2006) and other scoring systems (Fearon et al., 2002).

Fractional Flow Reserve

On the basis of pressure-flow analysis of coronary stenosis under maximal hyperemia, Pijls and De Bruyne (1996) introduced the concept of myocardial fractional flow reserve (FFR) as an invasively determined index of the functional severity of coronary stenoses (Pijls et al., 1993; De Bruyne, Baudhuin et al., 1994; De Bruyne, Paulus et al., 1994). Since its introduction, FFR has been compared to stress testing techniques, and to the very widely used, exercise ECG testing.

After the early work of Pijls and De Bruyne in the mid-90s correlating FFR and EET (De Bruyne et al., 1995; Pijls et al., 1995; Pijls et al., 1996), no new work has been undertaken for evaluating non-invasive testing compared to FFR. The most recent work was that of Tanaka et al., (2009) who evaluated FFR in stress testing (as the maximum of oxygen consumption) in patients with stable angina pectoris and lesions over 75% of vessel diameter.

Regarding the wide usage of EET and DTS, we have determined that a more detailed examination of borderline lesions and intermediate DTS compared to FFR, which is regarded nowadays as the gold standard in verifying ischemic lesions on coronary arteries, is necessary.

MATERIALS AND METHODS

Population

Thirty patients with a single lesion (30 lesions) were chosen using the following inclusion criteria: previous exercise stress testing with -10≤DTS≤4, angiographic findings of single lesion coronary disease between 30-70% of diameter stenosis, clinical status: Canadian Cardiovascular Society (CCS) class I-III and New York Heart Association (NYHA) I-II.

The following patients were excluded: recanalized lesions on previously myocardial infarct-related artery, coronary arteries under 2 mm diameter, multiple serial single vessel lesions, patients with significant multivessel disease (over 30% in any other artery), patients with unstable angina and/or worsening functional status, patients with left ventricular hypertrophy, aortic stenosis, patients on current digitalis therapy, electrolyte imbalance, EF<40%, and/

or any other factor that could impede exercise stress testing or FFR measurement.

All these patients had a prior functional assessment with an exercise stress test. Exercise stress tests were performed and DTS calculated as previously described.

Coronary angiography

Coronary angiography was performed using the radial or femoral approach with standard catheters and conventional views.

Quantitative coronary angiography (QCA)

The quantitative analysis of selected coronary segments was carried out with the help of a computer-based Siemens Axiom Artis System.

Coronary pressure measurement

Coronary pressure measurement was performed with a 0.014-in. pressure wire (Radi Medical Systems, Uppsala, Sweden). The wire was calibrated, equalized at the end of the guiding catheter, advanced into the coronary artery, and positioned about 3 cm distal to the stenosis as previously described (Pijls et al., 1996). Maximal hyperemia was induced by intracoronary administration of adenosine (140 μg for the left coronary artery and 60 μg for the right coronary artery) after i.c. bolus of nitroglycerine (200 μg for the left and 100 μg for the right coronary artery). FFR was calculated as the ratio of mean hyperemic distal coronary pressure measured by the pressure wire to mean aortic pressure measured by the guiding catheter.

Statistical considerations

Values of the examined parameters were analyzed using descriptive statistics, as mean and standard deviation. Statistical significance was defined at a *P* value of <0.05. For comparison, analysis of variance (ANOVA) and Bonferroni test for multiple comparisons were used. Comparison of two values of the same description was performed using the paired T test. Correlation was calculated using Pearson's correlation coefficient. Univariant and multivariant linear regression was used for the determination of single or multiple variables to outcome. The effect of more variables to the binary outcome was determined using multivariant binary logistic regression. Whether a single variable could serve as a marker for a certain outcome, a ROC (receiver operating characteristics) curve was used and cut-off values determined, along with specificity and sensitivity. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) statistical software.

RESULTS

In the study group, the average age was 58, with regular sex distribution. Average stenosis diameter was angiographically slightly higher than determined by QCA. The prevalence of risk factors such as hypertension, hypercholesterolemia, smoking, family history of CAD and diabetes mellitus was relatively high (Table 1). The most frequent lesions were in the left anterior descending artery (LAD) with the lowest FFR value (Table 2 and Fig. 1). The decision to perform revascularization (PCI in our case) is more often than not conflicted prior to and after FFR measurement (Table 3a and 3b). DTS showed good prognostic values (sensitivity=0.769 and specificity=0.556) only with a narrower range (under -0.5) (Fig 2.). There was no difference in mean DTS values between the sexes (Fig. 3.), a negative correlation was found between DTS values and age (r=0.131 p=0.491), but a positive correlation was found between angiographic assessment and QCA (Fig 4.) and FFR values and age (Fig 5.).

DISCUSSION

There is moderate accuracy in angiographically assessed coronary stenosis (Mintz et al., 1995) and hence with decision to perform PCI, despite guidelines for adequate QCA measurement (Scanlon et al., 1999). In our study, the correlation between these methods was significant (Fig. 4.), probably because they are both based on the same technique – luminography.

Table 1. Baseline characteristics

	N
Number	30
Age	58.7±5.71
Men/women	15/15
Systemic hypertension	21 (70%)
Hypercholesterolemia	18 (60%)
Diabetes mellitus	4 (13.33%)
Smoking	16 (53.33%)
Family history of CAD	12 (40%)
DS-A (%)	53.50±8.82
DS-QCA (%)	48.40±6.99
FFR	81.43±8.57
DTS	-0.87±3.88

Values are presented as the % or mean ± standard deviation.

Table 2. Distribution of lesions on site of coronary artery

Coronary segment	Frequency	Percentage
LADo	2	6.7
LADp	9	30.0
LADm	7	23.3
LCXo	1	3.3
LCXp	1	3.3
LCXm	1	3.3
LCXd	1	3.3
RCAm	1	3.3
RCAd	1	3.3
PD	1	3.3
RI	1	3.3
DG	3	10.0
OM	1	3.3
Total	30	100,0

LAD – left anterior descending coronary artery; DG – diagonal branch; LCX – left circumflex artery; OM – obtuse marginal artery; RI – intermediate branch (ramus intermedius); RCA – right coronary artery. Segments: o – ostial;, p – proximal; m – medial; d – distal.

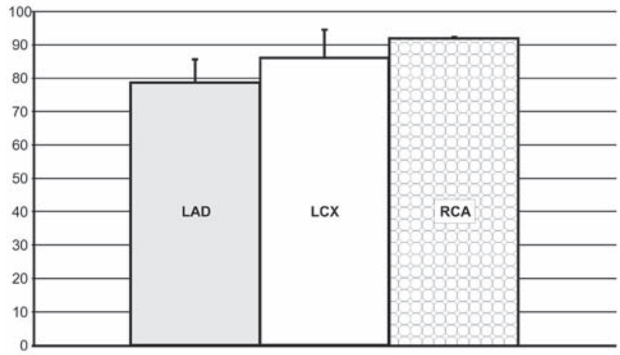

Fig. 1. Mean values of FFR between coronary arteries. Bonferroni test showing significant difference between LAD and RCA (p=0.026), indicating the difference between LAD and LCx (0.059).

Table 3a. Initial decision to perform PCI based on angiographic assessment

Descission	Frequency	Percentage
Defer	10	33.3
PCI	20	66.7
Total	30	100.0

Table 3b. Decision to perform PCI after FFR measurement

Descission	Frequency	Percentage
Defer	22	73.3
PCI	8	26.6
Total	30	100.0

Not surprisingly, a decision based on angiography to perform PCI is predominantly in favor of PCI (70% vs. 30%), leading to many unnecessary PCI (lesion treated are non-ischemic) (Table 3a and 3b).

Our study showed a weak diagnostic value of DTS (Fig. 2.) within the range that was considered intermediate. The complex mechanism of ST depression is the main limitation of EET. The classical theory of ST depression is subendocardial ischemia due to partial (dynamic) occlusion of one or more coronary arteries. Earlier studies have proven the connection of zone subendocardial ischemia to concomitant leads in ECG (MacLachlan et al., 2005). The latest *in vitro* studies (Potse et al., 2007), with a much more realistic model of myocardial ischemia, have shown maximal ST depression in the region around the directly affected ischemic region. Contrary to ST elevation, ST depression (induced or spontaneous) has poor spatial resolution and is a lot less confined to the ischemic region. Animal models (Li et al., 1998; Kilpatrick et al., 2003; De Chantal et al., 2006) have shown that partial occlusion of the artery does not lead to marked ST depression. Therefore, a new hypothesis is that ST depression does not represent a regional, but rather a global subendocardial ischemic phenomenon, occurring during an exercise- or stress-induced shortening of the diastolic

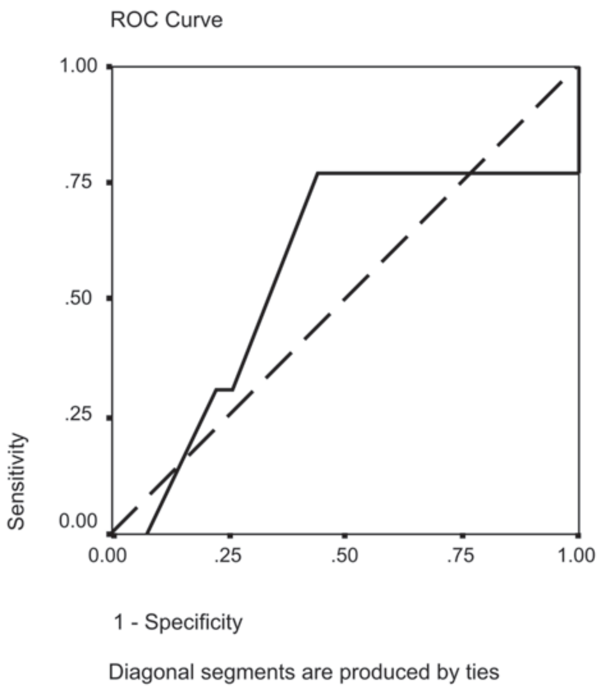

Fig. 2. ROC curve at standard values of DTS – AUROC 0.563, p=0.525. Adequate specificity and sensitivity (0.769 and 0.556 respectively) are at values under -0.5.

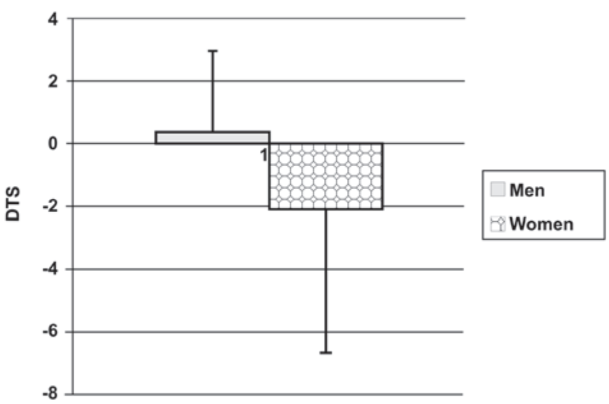

Fig. 3. Mean values of DTS between sexes (p=0.073).

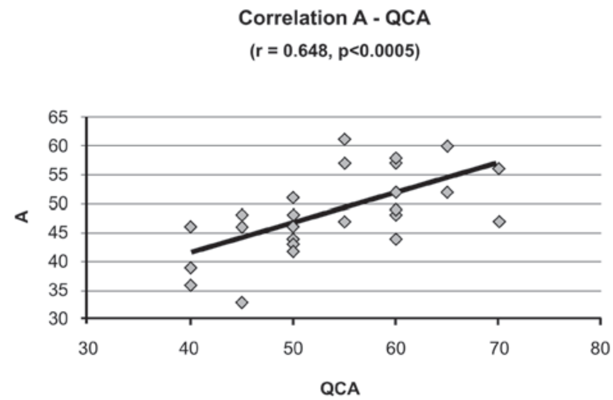

Fig. 4. Correlation between QCA and angiographic assessment.

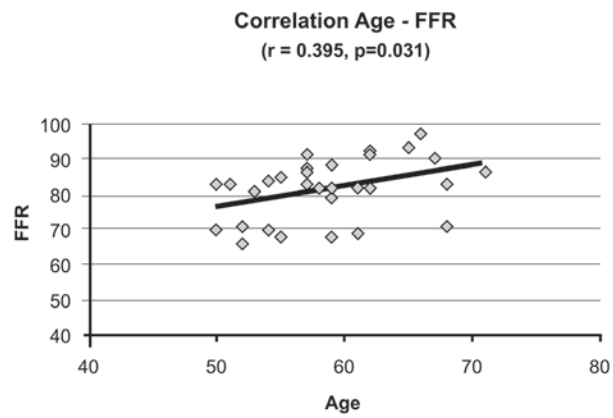

Fig. 5. Correlation between age and FFR values.

filling and elevated end-diastolic pressure. Therefore, localization of ST depression is not dependant on the region of ischemic myocardium (region vascularized by the given artery). Another study (Hopenfeld et al., 2004) using a computer model presumed that ST depression is formed due to an electric circuit starting and completing at the lateral edge between the ischemic and non-ischemic myocardium and flowing via transmural connection between the two. The electric current is a consequence of the more negative transmembrane potential of ischemic to non-ischemic zones. When the voltage between the zones is greater than between the transmural layers, a current is formed between the ischemic and non-ischemic zone within the lateral border. The result is an epicardial ST depression above the lateral border zone. In cases of multivessel disease, an electrode placed over the ischemic area may show a significantly smaller ST depression because of both ischemic regions contributing to the formation (Lew et al., 1985). The magnitude of the ST depression can be reduced during prolonged ischemia, and is related to the closing of the gap junctions (Smith et al., 1995). Despite various proposed mechanisms of ST depression formation, clinical implications are similar: maximal ST depression does not occur over the ischemic but over the borderline zone of the myocardium, and the magnitude and spatial resolution of the occurring ST depression can be attributed to various factors leading to subendocardial ischemia (hypertension, decreased LV compliance, microvascular coronary disease).

Considering the above, we have not paid much attention to the spatial distribution of a marked ST depression related to the culprit lesion. Considering the homogenous population of the study (single vessel disease), other contributing lesions were of no consequence. On the other hand, an impeded microvascular response was not considered, and the index of microvascular resistance was not calculated. Therefore, the contribution of impaired microvascular response (as in microvascular angina) in 'false' positive exercise testing remains to be assessed. The contribution of diffuse disease and/or spasm of diseased segment during FFR measurement is abolished by intracoronary injection of nitroglycerine. Finally, the interpretation of anginal pain is subjective regarding pain intensity and type.

Earlier studies have shown differences between the sexes in EET sensitivity and specificity. In females, test sensitivity and specificity are significantly lower (Mieres et al., 2005). Our study did not show statistical difference between the sexes, which is probably due to the small sample size.

The DTS has not been found to be a reliable predictor of cardiovascular mortality in elderly patients compared to the younger population (Kwok et al., 2002). We did not show the relation between DTS and age (r=0.131, p=0.491), which can be explained by the average age of the patients involved and the oldest patient being 71 years old. All of our patients had good functional status, without serious comorbidities, unlike the patient populations found in literature (Kwok et al., 2002; Gaul et al., 1984) .

On the other hand, we showed a positive correlation between FFR and age (Fig. 5.). A possible explanation is that in the elderly, due to the long-term effects of atherosclerosis, more collaterals (Simić et al., 2013) are found and, generally, reduced myocardial viability.

CONCLUSION

In the case of patients with single vessel disease and intermediary stenosis, the current range of Duke Treadmill Score where the test is considered intermediate (-10 to +4) has proven to be too wide. Narrowing the test criteria to under -0.5 would give the test adequate sensitivity and specificity.

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