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Review article

Non-invasive testing in chronic coronary syndrome - comparison between functional and anatomic approach

Vojislav Giga[1,2], Nikola Bošković[1], Ana Đorđević-Dikić[1,2] , Ivana Nedeljković[1, 2], Branko Beleslin[1,2]

[1] Cardiology Clinic, University Clinical Center of Serbia, [2] Faculty of Medicine, University of Belgrade

Abstract For the decades, functional testing has been a cornerstone of non-invasive diagnosis and risk stratification in patients with chronic coronary syndromed. With technological improvements coronary CT angiography (CTA) became alterntative method for the assessment of coronary circulation. The aim of this review paper is to show the advantages and limitations of both tecniques and to demonstrate their complementary nature.CTA and functional tests represent complementary methods for the evaluation of patients with chest pain, whereas each method has its place in the diagnostic algorithm. Functional tests are indicated in patients with high clinical probability for the presence of obstructive coronary artery disease for the confirmation of the disease and risk stratification. CTA is indicated in patients with lower clinical probability for the presence of obstructive coronary artery disease when the exclusion of the disease is the major intention. Also, it can be used in patients with chest pain and previous negative functional test in order to establish the presence of non-obstructive vulnerable plaques in order to initiate cardioprotective therapy and prevent future events.

Key words CT coronary angiography, functional testing

For the decades, functional testing has been a cornerstone of non-invasive diagnosis and risk stratification in patients with chronic coronary syndromed. With technological improvements coronary CT angiography (CTA) became alterntative method for the assessment of coronary circulation. The aim of this review paper is to show the advantages and limitations of both tecniques and to demonstrate their complementary nature.

Two recent, randomized studies, PROMISE1 and SCOT-HEART[2], compared prognostic value of functional and anatomical non-invasive testing in patients with chest pain, with pre-test probability for the presence of coronary artery disease of 53%. Patients were randomized on functional testing (68% perfusion scintigraphy, 22% stress echocardiography and 10% stress electrocardiography) or CTA. Half of the patients were women, whereas ¾ of patients had atypical chest pain. The prevalence of obstructive disease on CTA was 11.9% and positive finding on functional test was present in 12.6% of patients. Such a low prevalence of positive functional test is typical in contemporary patients, and can partially be explained by the higher number of patients with atypical symptoms reffered to functional testing as well as with the fact that even in patients with typical symptoms the prevalence of obstructive coronary artery disease is rather low[3]. During the median follow-up of 25 months, there was no significant difference in primary outcome (all-cause mortality, myocardial infarction, unstable angina requiring hospitalization and complications of cardiovascular procedures) between functional (3.0%) and CTA arm (3.3%) of the study.

Data from PROMISE trial clearly demonstrated that the abnormal findings (presence of obstructive stenosis) on non-invasive testing carries poor prognosis, with 3.5 times higher risk of adverse events in comparison to patients with normal findings[4].

On the other hand, patients with completely normal finding on CTA (0% of stenosis) or on functional testing have excellent prognosis. Prevalence of adverse events after negative CTA was 0.93%, confirming further superb negative predictive value of almost 99%[4,5,6]. After negative functional test prevalence of adverse cardiac events was higher (2.09%) in comparison to negative CTA. However, it has been demonstrated that the incidence of obstructive coronary artery disease is increasing in patients with multiple risk factors (Framingham risk score above 20%) even after negative functional test. At contrary incidence of obstructive coronary artery decreases in patients with Framingham risk score below 10% even after positive functional test. If the normal finding on functional test in PROMISE population is defined as the absence of inducible ischemia only in patients with Framingham risk score < 10%, rate of adverse event is almost identical to that of negative CTA (0.92% vs. 0.93%) and corresponds to previously published data[7].

There are several explanations for adverse events after negative functional test, including false negative reading due to low workload and heart rate during test, presence of single vessel disease (especially circumflex artery), drug therapy that modify heart rate and ischemia, and finally presence of balanced ischemia in multi-ves-

Address for correspondence: Vojislav Giga, MD, PhD, Cardiology Clinic, University Clinical center of Serbia; Faculty of Medicine, University of Belgrade.
E-mail: voja2011@yahoo.com

sel disease that is highly relevant mechanism in patients undergoing perfusion scintigraphy. Also, the occurrence of late events can be explained by the progression of the disease itself. In PROMISE trial in patients randomized to functional testing the majority of events occurred in the group of the patients with severe inducible ischemia (large extent of ischemia in LAD territory, or in the territory of other artery with concomitant decrease in EF below 35%, or the presence of ischemia in ≥ 2 territories). The larger the extent of ischemia is, the higher is the risk of adverse events. These findings from PROMISE trial once again confirms the excellent ability of functional test to identify severe coronary artery disease, so this approach is recommended in patients with high clinical probability for the presence of obstructive coronary artery disease.

The major limitation of functional tests is their limited ability to predict the occurrence of acute thrombotic coronary artery occlusion, especially in the presence of mild coronary atherosclerosis. In PROMISE trial absolute number of adverse events was the highest in patients with negative functional test[4], and the explanation is that these events are due to the rupture of nonsignificant plaques that are unable to cause myocardial ischemia detectable with functional test. According to the results of PROMISE trial in patients randomized to CTA the majority of events was in patients with non-obstructive coronary atherosclerosis (stenosis 1-69% in main or side branch or left main stenosis < 50%). The occurrence of acute thrombosis is due to the rupture of vulnerable plaques with thin fibrous cap and large lipid core. The major advantage of CTA is the ability to detect those vulnerable plaques with low attenuation. The risk for plaque rupture and consequent acute coronary event increases with the increase in vulnerable plaques burden. Data form SCOT-HEART study clearly showed that the presence of more than 4% of vulnerable plaques on CTA is related to five times higher risk of fatal or non-fatal myocardial infarction[8]. Similarly is observed in PROMISE trial. The presence of high risk plaques increases risk of adverse cardiovascular events for 70%, irrespective of the presence of other risk factors and the presence of obstructive coronary artery disease. The identification of such plaques is especially important in younger patients and in women with low atherosclerotic burden[9]. That is the reason why CTA is method of choice in patients with chest pain and lower clinical probability of obstructive disease in which negative finding on functional test is expected, but risk of thrombotic events is present. It has been shown in PROMISE trial that 6.5% of vulnerable plaques are prone to rupture[9]. The ability of CTA to detect non-obstructive vulnerable plaques represent the most important explanation for the superiority of CTA in comparison to functional testing (85% of exercise electrocardiography) in the detection of patients at risk of cardiac death or non-fatal myocardial infarction during the 5 years follow-up period (2.3% vs. 3.9%)[2]. It has to be kept in mind that the rate of revascularization was similar between the groups, so the benefit of CTA based approach is predominantly driven by the higher use of cardioprotective drugs (aspirin and statin) (10). The similar pattern of cardioprotective use that leads to plaque stabilization and the prevention of adverse events is also observed in PROMISE trial (11).

Conclusion

CTA and functional tests represent complementary methods for the evaluation of patients with chest pain, whereas each method has its place in the diagnostic algorithm. Functional tests are indicated in patients with high clinical probability for the presence of obstructive coronary artery disease for the confirmation of the disease and risk stratification. CTA is indicated in patients with lower clinical probability for the presence of obstructive coronary artery disease when the exclusion of the disease is the major intention. Also, it can be used in patients with chest pain and previous negative functional test in order to establish the presence of non-obstructive vulnerable plaques in order to initiate cardioprotective therapy and prevent future events.

It should be kept in mind that further testing is not indicated in patients with non-anginal chest pain and normal ECG. Overall, the prognosis of such patients is good with low incidence of fatal and non-fatal myocardial infarction of 0.5% annually[12].

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Sažetak

Neinvazivni testovi u hroničnom koronarnom sindromu - poređenje funkcionalnog i anatomskog pristupa

Vojislav Giga[1,2], Nikola Bošković[1], Ana Đorđević-Dikić[1,2] , Ivana Nedeljković[1, 2], Branko Beleslin[1,2]

[1]Klinika za kardiologiju, Univerzitetski klinički centar Srbije, [2]Medicinski fakultet, Univerzitet u Beogradu

Dugo vremena neinvazivni funkcionalni testovi su imali vodeću ulogu u dijagnostici i stratifikaciji rizika kod bolesnika sa hroničnim koronarnim sindromom. Međutim, sa tehničkim usavršavanjem, CT koronarna angiografija zauzima važno mesto u neinvazivnoj proceni bolesnika sa bolom u grudima. CT koronarna angiografija i funkcionalni testovi su komplementarne metode u evaluaciji bolesnika sa bolom u grudima, pri čemu svaka ima svoje mesto u dijagnostičkom algoritmu. Funkcionalni testovi su indikovani kod bolesnika sa visokom kliničkom verovatnoćom za postojanje obstruktivne koronarne bolesti, gde testovi potvrđuju dijagnozu i omogućavaju stratifikuju rizika. CT koronarna angiografija je indikovana kod bolesnika sa nižom kliničkom verovatnoćom za postojanje obstruktivne koronarne bolesti kod kojih želimo prvenstveno isključiti prisustvo kornonarne bolesti , a može se razmotriti kod osoba i nakon negativnih funkcionalnih za identifikaciju rasprostranjenosti i karakteristika neobstruktivnih aterosklerotskih plakova i pravovremeno započinjanje kardioprotektivne terapije.

Ključne reči: *CT koronarna angiografija, funkcionalni testovi*