Nebivolol in patients with coronary slow flow: the right drug for the right case?

Koroner yavaş akımlı hastalarda nebivolol: Doğru vaka için doğru ilaç mı?

Coronary slow flow has been long recognized as an aspecific angiographic pattern in different cardiac conditions. Among the others, it is often observed in patients with normal coronary arteries. Several studies have suggested that increased sympathetic outflow to the cardiovascular system may be responsible for both symptoms and electrocardiographic changes (1-3) that occur in patients with angina pectoris, positive exercise test and angiographically smooth coronary arteries (cardiac syndrome X). Because the autonomic nervous system plays a pivotal role in the regulation of coronary blood flow, increased sympathetic activity could account for both primary reduction of coronary blood flow (4) and reduced vasodilator reserve, which is observed in some patients with syndrome X (5). In these patients, beta-blockade with atenolol has been previously shown to normalize QT interval and dispersion, 2 markers of sympathetic activity (6). However, despite beta-blockade with traditional agents has been previously shown to yield several favourable effects (7), some pharmacological properties of conventional beta-blockers could make them not ideal in patients with syndrome X, especially in those patients exhibiting increased arteriolar resistance. In fact, apart from reducing sympathetic activity, most selective beta-blockers decrease insulin sensitivity, increase blood lipid levels and reduce endothelial function (8-12). More specifically, endothelial dysfunction could be the cause of reduced progression of the angiographic dye (coronary slow flow) observed in some patients with angina and normal coronary arteries. Since endothelial dysfunction (13) and slow flow (14) have been associated to worse prognosis, the identification of more appropriate therapies for these clinical syndromes would be envisaged.

In the present issue of the Anatolian Journal of Cardiology, Güneş and colleagues have evaluated the effects of a new generation beta-blocker, nebivolol, in a population of patients with coronary slow flow (15), undergoing coronary angiography because of suspected coronary artery disease (angina and/or positive exercise testing). In this study, 3 months treatment with nebivolol has been shown to improve atrial indexes of autonomic nervous control and Doppler left ventricular filling pattern. The hypothesis is that these functional and electrophysiological improvements depend on the beneficial effects exerted by nebivolol in terms of prevention of myocardial ischemia, through a mixed anti-adrenergic and endothelial function improvement mechanism.

This is an interesting study for two distinct reasons. First, it confirms the negative electrophysiological effects of an often underestimated angiographic pattern, the so-called "coronary slow-flow phenomenon". Turkish cardiologists have been traditionally very active in studying various clinical contexts in which this angiographic pattern is evidenced and investigating several clinical characteristics associated to its occurrence (16-24). Nevertheless, coronary slow flow is often (worldwide) dismissed as a trivial and benign angiographic finding, even though substantial evidence seems to indicate the contrary (14, 25-26). In fact, this phenomenon has been also associated with serious arrhythmic risk (27), and, despite several therapies have been proposed for its treatment, no systematic studies in this sense have been performed so far. This is indeed the second reason of interest of Güneş et al. study (15), where the effects of nebivolol, a new generation beta-blocker, have been evaluated in a population of patients with coronary slow flow. The observed beneficial electrophysiological and functional effects of nebivolol in these patients are not surprising, if one takes into consideration the pathophysiology of coronary slow flow and the mechanism of action of this new beta-blocker. In fact, apart from the highly selective antagonism of β_1-adrenergic receptors, nebivolol also dilates arteries by mechanisms involving nitric oxide (NO) (28). The mechanism of vasodilator action of nebivolol is attributed largely to activation of endothelial NO synthase in vascular endothelial cells (28), which seem to be strongly involved in the pathogenesis of microvascular dysfunction (29-30). Therefore, the paper of Güneş et al. suggests that nebivolol can be considered an effective new therapeutic tool in the management of patients with angina, angiographical normal

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coronary arteries and coronary slow flow who, on the other hand, are often very symptomatic and may carry a prognosis not as good as that of similar patients not presenting slow flow. However, further studies are warranted to evaluate the long-term prognostic implications of coronary slow flow and the potential clinical effects of nebivolol in this context.

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References

1. Montorsi P, Manfredi M, Loaldi A, Fabbiocchi F, Polese A, de Cesare N, et al. Comparison of coronary vasomotor responses to nifedipine in syndrome X and Prinzmetal's angina pectoris. Am J Cardiol 1989; 63: 1198-202.
2. Montorsi P, Cozzi S, Loaldi A, Fabbiocchi F, Polese A, De Cesare N, et al. Acute coronary vasomotor effects of nifedipine and therapeutic correlates in syndrome X. Am J Cardiol 1990; 66: 302-7.
3. Galassi AR, Kaski JC, Crea F, Pupita G, Gavrielides S, Tousoulis D, et al. Heart rate response during exercise testing and ambulatory ECG monitoring in patients with syndrome X. Am Heart J 1991; 122: 458-63.
4. Kaski JC, Crea F, Nihoyannopoulos P, Hackett D, Maseri A. Transient myocardial ischemia during daily life in patients with syndrome X. Am J Cardiol 1986; 58: 1242-7.
5. Greenberg MA, Grose RM, Neuburger N, Silverman R, Strain JE, Cohen MV. Impaired coronary vasodilator responsiveness as a cause of lactate production during pacing-induced ischemia in patients with angina pectoris and normal coronary arteries. J Am Coll Cardiol 1987; 9: 743-5.
6. Leonardo F, Fragasso G, Rosano GM, Pagnotta P, Chierchia SL. Effect of atenolol on QT interval and dispersion in patients with syndrome X. Am J Cardiol 1997; 80: 789-90.
7. Chierchia SL, Fragasso G. Angina with normal coronary arteries: diagnosis, pathophysiology and treatment. Eur Heart J 1996; 1 7 (Suppl G): 14-9.
8. Giugliano D, Acampora R, Marfella R, De Rosa N, Ziccardi P, Ragone R, et al. Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension. A randomized, controlled trial. Ann Intern Med. 1997; 126: 955-9.
9. Fragasso G, Cattaneo N, Locatelli M, Caumo A, Pagnotta P, Piatti P, et al. Differential effects of selective beta-adrenergic blockade on insulin sensitivity and release in control subjects and in patients with angina and normal coronary arteries (syndrome X). G Ital Cardiol 1998; 28: 623-9.
10. Poirier L, Cléroux J, Nadeau A, Lacourcière Y. Effects of nebivolol and atenolol on insulin sensitivity and haemodynamics in hypertensive patients. J Hypertens 2001; 19: 1429-35.
11. Olsen MH, Fossum E, Høieggen A, Wachtell K, Hjerkinn E, Nesbitt SD, et al. Long-term treatment with losartan versus atenolol improves insulin sensitivity in hypertension: ICARUS, a LIFE substudy. J Hypertens 2005; 23: 891-8.
12. Lithell HO. Effect of antihypertensive drugs on insulin, glucose, and lipid metabolism. Diabetes Care 1991; 14: 203-9.
13. Bugiardini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease: a study on women with chest pain and normal angiograms. Circulation 2004; 109: 2518-23.
14. Fragasso G, Chierchia SL, Arioli F, Carandente O, Gerosa S, Carlino M, et al. Coronary slow-flow causing transient myocardial hypoperfusion in patients with cardiac syndrome X: long-term clinical and functional prognosis. Int J Cardiol. 2008 Aug 30. [Epub ahead of print])
15. Güneş Y, Tuncer M, Güntekin Ü, Ceylan Y. The effects of nebivolol on p wave duration and dispersion in patients with coronary slow flow. Anadolu Kardiyol Derg 2009; 290-5
16. Yazıcı M, Demircan S, Aksakal E, Şahin M, Meriç M, Dursun I, et al. Plasma insulin, glucose and lipid levels, and their relations with corrected TIMI frame count in patients with slow coronary flow. Anadolu Kardiyol Derg 2003; 3: 222-6.
17. Yazıcı M, Aksakal E, Demircan S, Şahin M, Sağkan O. Is slow coronary flow related with inflammation and procoagulant state? Anadolu Kardiyol Derg 2005; 5: 3-7.
18. Özcan T, Gen R, Akbay E, Horoz M, Akçay B, Gençtoy G, et al. The correlation of thrombolysis in myocardial infarction frame count with insulin resistance in patients with slow coronary flow. Coron Artery Dis 2008; 19: 591-5.
19. Yılmaz H, Demir I, Uyar Z. Clinical and coronary angiographic characteristics of patients with coronary slow flow. Acta Cardiol 2008; 63: 579-84.
20. Nurkalem Z, Alper AT, Orhan AL, Zencirci AE, Sarı I, Erer B, et al. Mean platelet volume in patients with slow coronary flow and its relationship with clinical presentation. Turk Kardiyol Dern Ars 2008; 36: 363-7.
21. Acar G, Akçay A, Nacar AB, Tuncer C. Coronary artery fistula associated with slow coronary flow: a rare cause of myocardial ischemia. Anadolu Kardiyol Derg 2008; 8: E32-3.
22. Şen N, Başar N, Maden O, Özcan F, Özlü MF, Güngör O, et al. Increased mean platelet volume in patients with slow coronary flow. Platelets 2009; 20: 23-8.
23. Nurkalem Z, Görgülü S, Uslu N, Orhan AL, Alper AT, Erer B, et al. Longitudinal left ventricular systolic function is impaired in patients with coronary slow flow. Int J Cardiovasc Imaging 2009; 25: 25-32.
24. Nurkalem Z, Tangürek B, Zencirci E, Alper AT, Aksu H, Erer B, et al. Endothelial nitric oxide synthase gene (T-786C) polymorphism in patients with slow coronary flow. Coron Artery Dis 2008; 19: 85-8.
25. Diver DJ, Bier JD, Ferreira PE, Sharaf BL, McCabe C, Thompson B, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA Trial). Am J Cardiol 1994; 74: 531-7.
26. Kapoor A, Goel PK, Gupta S: Slow coronary flow-a cause for angina with ST segment elevation and normal coronary arteries: a case report. Int J Cardiol 1998; 67: 257-61.
27. Saya S, Hennebry TA, Lozano P, Lazzara R, Schechter E. Coronary slow flow phenomenon and risk for sudden cardiac death due to ventricular arrhythmias: a case report and review of literature. Clin Cardiol 2008; 31: 352-5.
28. Cockroft JR, Chowienczyk PJ, Brett AE, Chen CPLH, Dupont AG, Nueten LV, et al. Nebivolol vasodilates human forearm vasculature: evidence for an -arginine/NO-dependent mechanism. J Pharmacol Exp Ther 1995; 274: 1067-71.
29. Piatti PM, Fragasso G, Monti LD, Caumo A, Phan VC, Valsecchi G, et al. Endothelial and metabolic characteristics of patients with angina and angiographically normal coronary arteries. J Am Coll Cardiol 1999; 34: 1452-60.
30. Piatti PM, Fragasso G, Monti LD, Setola E, Lucotti P, Fermo I, et al. Acute intravenous L-arginine infusion decreases endothelin-1 levels and improves endothelial function in patients with angina pectoris and normal coronary arteriograms: correlation with asymmetric dimethylarginine levels. Circulation 2003; 107: 429-36.