Effect of *Diltiazem* on Coronary Artery Flow and Myocardial Perfusion in Patients With Isolated Coronary Artery Ectasia and Either Stable Angina Pectoris or Positive Myocardial Ischemic Stress Test

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Isolated coronary artery ectasia (CAE) may be associated with stable or unstable coronary events despite the absence of epicardial coronary stenosis. Impaired coronary flow dynamics and myocardial perfusion have been demonstrated in stable patients with ectatic coronary arteries. We aimed to assess whether epicardial flow and tissue-level perfusion would be improved by diltiazem in myocardial regions subtended by the ectatic coronary arteries in patients with isolated CAE. A total of 60 patients with isolated CAE were identified of 9,780 patients who underwent elective coronary angiography. Patients were randomized to 5 mg of intracoronary diltiazem or saline. Coronary blood flow of the microvascular network was assessed using myocardial blush grade (MBG) technique. The thrombolysis in myocardial infarction (TIMI) flow grade and TIMI frame count (TFC) were used to assess epicardial coronary flow. MBG (from 2.4 to 2.6, $p = 0.02$), TIMI flow grades (from 2.4 to 2.8, $p < 0.001$), and TFC (from 35 to 26, $p < 0.001$) were significantly improved after diltiazem, whereas no significant change was noticed after saline (from 2.4 to 2.4, $p = 0.86$ for MBG; from 2.3 to 2.3, $p = 0.71$ for TIMI flow grade; and from 35 to 33, $p = 0.43$ for TFC). Diltiazem provided amelioration of the altered coronary flow dynamics, which was suggested as the pathophysiological influence of CAE. In conclusion, the favorable effects of the diltiazem on myocardial perfusion were observed at both epicardial and tissue levels. **(Am J Cardiol 2015;116:1199−1203)**

The present study with prospective randomized design was set up to assess whether epicardial flow and tissue-level perfusion would be improved by diltiazem in myocardial regions subtended by the ectatic coronary arteries in patients with isolated coronary artery ectasia (CAE).

Methods

This report complies with Consolidated Standards of Reporting Trials (CONSORT) statement.[1] Nine thousand seven hundred and eighty patients who underwent elective coronary angiography at the Ankara University Department of Cardiology from June 2012 to April 2015 were examined for CAE. The overall incidences of CAE and isolated CAE were 3.8% (368 of 9,780 patients) and 0.83% (81 of 9,780 patients), respectively. The detailed flow diagram of participants is shown in Figure 1. Stratified block randomization was preferred, in which method age, gender, and ectatic vessel were determined as stratification factors. Randomization was performed by a researcher different from the operator of the coronary angiography. Neither the randomization researcher nor the participant was informed about which group the participant was in until the measurements had completed at the end of the study. Patients were eligible if they had isolated CAE and stable angina pectoris or positive ischemia on stress tests. The primary outcome measure of the study was specified as myocardial blush grade (MBG) which indicated the degree of myocardial microvascular perfusion. The secondary outcome measure was determined as thrombolysis in myocardial infarction (TIMI) flow grade and TIMI frame count (TFC) which demonstrated the level of coronary epicardial flow.

All the patients gave written informed consents. This study complied with the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002, was reviewed and approved by the institutional ethics committee on human research and registered at ClinicalTrials.gov (identifier NCT02024919). All vasoactive medications were interrupted 24 hours before coronary angiography. Patients with acute coronary syndrome, significant valvular heart disease, heart failure, systolic blood pressure $\leq$90 mm Hg, heart rate $\geq$60, atrioventricular block (grade $\geq$ II), severe liver or kidney failure, significant coronary artery stenosis, and known allergy to diltiazem were excluded.

The indications of coronary angiography were stable angina pectoris and/or positive stress test suggestive of myocardial ischemia. Coronary angiography was performed using the standard technique by means of the Judkins method

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See page 1203 for disclosure information.

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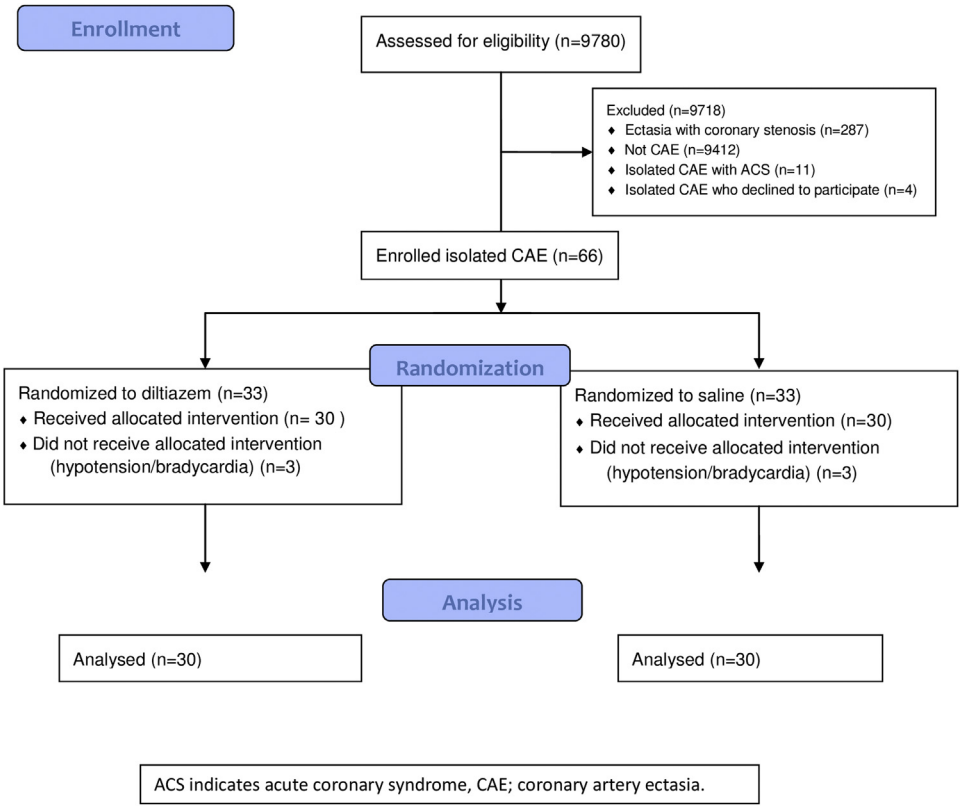

Figure 1. Flow diagram of patients. The diagram includes detailed information on the excluded patients.

Table 1
Comparison of baseline demographic and clinical characteristics of both groups

Characteristics	Diltiazem (n=30)	Saline (n=30)	P
Age, (years ± SD)	57±12	59±12	0.57
Male sex	21(70%)	23(77%)	0.77
Left ventricular ejection fraction, (% ± SD)	61±5	63±6	0.31
Hypertension	21(70%)	17(57%)	0.42
Diabetes mellitus	7(23%)	9(30%)	0.30
Smoker	11(37%)	13(43%)	0.79
Body mass index, (kg/m^2 ± SD)	27±3	26±4	0.66
Fasting blood glucose, (mg/dl ± SD)	110±34	114±27	0.73
Total cholesterol, (mg/dl ± SD)	179±47	175±51	0.74
LDL cholesterol, (mg/dl ± SD)	101±31	99±44	0.88
HDL cholesterol, (mg/dl ± SD)	40±7	42±10	0.42
Triglyceride, (mg/dl ± SD)	170±82	158±88	0.28
Creatinine, (mg/dl ±SD)	0.94±0.3	0.89±0.2	0.46
Hemoglobin, (g/dl ± SD)	14.7±1.7	14.1±2.0	0.23
Baseline medications			
Beta blockers	18(60%)	15(50%)	0.60
Statins	26(87%)	21(70%)	0.21
ACEi /ARB	20(67%)	17(57%)	0.59
Ectatic coronary artery			
Left Anterior Descending	9(30%)	9(30%)	1
Circumflex	6(20%)	5(17%)	0.89
Right	15(50%)	16(53%)	0.94

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; HDL = high density lipoprotein; LDL = low density lipoprotein.

with 6F diagnostic catheters (Boston Scientific, Boston, Massachusetts) without use of nitroglycerin. Coronary blood flow of the microvascular network was assessed on compact disk films at 30 frames (Siemens Artis Zee, Siemens AG, Medical Solutions, Erlangen, Germany) by 2 observers who were blinded to patients' clinical data, using the MBG technique, as previously described[2]: grade 0, no myocardial blush; grade 1, minimal blush; grade 2, moderate myocardial blush, but less than that obtained in the same coronary territory of an age- and sex-matched control participant; grade 3, normal myocardial blush. The TIMI flow grade and TFC were assessed for each vessel using criteria defined by Chesebro et al[3] and Gibson et al,[4] respectively. The number of cineframes required for contrast to reach standardized distal coronary landmarks was measured. The distal coronary landmarks used for analysis were the distal bifurcation at the apex of the left anterior descending coronary artery, the distal bifurcation of the major obtuse marginal, or the main circumflex coronary artery, whichever was larger, and the site of origin of first branch at the crux for the right coronary artery. The left anterior descending coronary artery frame counts were corrected by dividing by 1.7 to obtain the corrected TFC as described earlier.[4] Angiographic runs had to be long enough to allow filling of the venous coronary system, and backflow of the contrast agent into the aorta had to be present, to be certain of adequate contrast filling of the epicardial coronary artery. Interobserver and intraobserver variabilities were determined from a random sample of 20 coronary territories scored by reviewers. After allocation of