

of the risk factors will lead to gene-informed personalized prevention (2). It is thus important to identify genes that confer susceptibility to coronary artery disease (CAD). Furthermore, stratification of subjects based on conventional risk factors for CAD and prospective cohort studies are also important to accomplish personalized medicine. In our study (1), low-risk individuals were defined as those who did not have any of the three major risk factors (hypertension, diabetes mellitus, and hypercholesterolemia). Given that the study is a cross-sectional association study, the classification of subjects as low-risk or high-risk was not based on the prevalence of myocardial infarction (MI) after follow-up of 10 years. Although a survivor bias could not be excluded completely, it was likely to be small in our study because of a relatively low prevalence of fatal MI (approximately 20%) in Japan. The variant alleles of four single nucleotide polymorphisms (SNPs) significantly associated with CAD are thus markers of predisposition to CAD.

Although the $-786\text{T}\rightarrow\text{C}$ SNP of the endothelial nitric oxide (eNOS) gene was related to CAD in the total population and in high-risk men, the *p* values were 0.0484 (additive model) and 0.0369 (dominant model), respectively (1). In an initial screening of the 112 polymorphisms for association with MI in 909 subjects in our previous study (3), the $-786\text{T}\rightarrow\text{C}$ SNP of eNOS gene was related to MI in men and women. In a large-scale association study, however, this SNP was not significantly associated with MI in men or women (3). The characteristics of ideal association study include a large sample size, small *p* values, an association that makes biological sense, and alleles that affect the gene product in a physiologically meaningful way (4). Two studies with a *p* value of <0.01 or a single study with a *p* value of <0.001 other than the first positive study is strongly predictive of future replication (5). Given that we adopted a criterion of a *p* value of <0.005 as statistical significance for association (1), the relation of the $-786\text{T}\rightarrow\text{C}$ SNP of eNOS gene with CAD was considered not to be significant. Although this SNP was shown to be associated with coronary artery spasm (6), the relation of this SNP with CAD remains to be elucidated.

In a stepwise forward selection procedure, four SNPs significantly associated with CAD were all statistically independent of age, smoking, or hyperuricemia as well as hypertension, diabetes mellitus, and hypercholesterolemia. As Drs. Rossi and Maiolino point out, the presence of hypertension, diabetes mellitus, and hypercholesterolemia may blunt nitric oxide availability. However, the $^{1019}\text{C}\rightarrow\text{T}$ SNP of the connexin-37 gene in high-risk men and the $^{3932}\text{C}\rightarrow\text{T}$ SNP of the apolipoprotein E gene in high-risk women were statistically independent of these risk factors.

Akihiro Hirashiki, MD

Yoshiji Yamada, MD, PhD

Department of Human Functional Genomics
Life Science Research Center
Mie University
1515 Kamihama
Tsu, Mie 514-8507
Japan
E-mail: yamada@gene.mie-u.ac.jp

Mitsuhiro Yokota, MD, PhD

REFERENCES

- Hirashiki A, Yamada Y, Murase Y, et al. Association of gene polymorphisms with coronary artery disease in low- and high-risk subjects defined by conventional risk factors. *J Am Coll Cardiol* 2003;42:1429–37.
- Braunwald E. Cardiology: the past, the present, and the future. *J Am Coll Cardiol* 2003;42:2031–41.
- Yamada Y, Izawa H, Ichihara S, et al. Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. *N Engl J Med* 2002;347:1916–23.
- Freely associating. Editorial. *Nat Genet* 1999;22:1–2.
- Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet* 2003;33:177–82.
- Nakayama M, Yasue H, Yoshimura M, et al. $\text{T}^{-786}\rightarrow\text{C}$ mutation in the 5'-flanking region of the endothelial nitric oxide synthase gene is associated with coronary spasm. *Circulation* 1999;99:2864–70.

Therapeutic Transcutaneous Ultrasound: Long Overdue Therapy

The recent report by Miyamoto et al. (1) presents the results of an experimental study evaluating the coronary vessel dilatory effect of transcutaneous low-frequency ultrasound. The investigators used a quite sophisticated animal model and demonstrated by various means that transcutaneous ultrasound induces vasodilation in canine coronary arteries. The magnitude of the effect was similar to that found with intracoronary nitrates. The researchers very correctly concluded that this phenomenon may be used as a therapeutic tool to reduce myocardial ischemia in patients with acute coronary syndromes.

Interestingly, in 1980 we first performed experimental and later clinical studies using approximately similar doses of transcutaneous ultrasound. The ultrasound frequency in our study was 790 to 910 kHz, with the ultrasound of 0.2 to 0.45 W/cm². The first case of transcutaneous ultrasound therapy in a patient was performed in early 1981 and later published in a USSR patent (2).

We completely agree with the editorial comments of Drs. McPherson and Holland (3) who postulated that this effect of ultrasound is strictly mechanical (acoustic radiation, streaming, and cavitation). Recently, we demonstrated that similar effects can be achieved with other forms of electromagnetic radiation (4,5).

In conclusion, we want to congratulate the investigators on a very interesting study, and we believe that further preclinical and clinical data may prove the safety and efficacy of this long overdue form of therapy, namely transcutaneous therapeutic ultrasound for treatment of ischemia.

Nicholas Kipshidze, MD, PhD

Lenox Hill Heart and Vascular Institute
130 East 77th Street
Black Hall, 9th Floor
New York, NY 10021
E-mail: nkipshidze@lenoxhill.net

Nodar N. Kipshidze, MD, PhD

National Center for Therapy
Tbilisi, Republic of Georgia

REFERENCES

1. Miyamoto T, Neuman Y, Luo H, et al. Coronary vasodilation by noninvasive transcutaneous ultrasound. *J Am Coll Cardiol* 2003;41:1623–7.
2. Kipshidze NN, Chapidze G, Shperling LV, et al. USSR patent no. 1172554: method for the treatment of patients with acute myocardial ischemia. January 18, 1982.
3. McPherson DD, Holland CK. Seizing the science of ultrasound: beyond imaging and into physiology and therapeutics. *J Am Coll Cardiol* 2003;41:1628–30.
4. Kipshidze N, Keelan MH, Petersen JR, et al. Photoactivation of vascular iNOS and elevation of cGMP in vivo: possible mechanism for photovaso-relaxation and inhibition of restenosis in an atherosclerotic rabbit model. *Photochem Photobiol* 2000;72:579–82.
5. Kipshidze N, Nikolaychik V, Keelan MH, et al. Low-power helium: neon laser irradiation enhances production of vascular endothelial growth factor and promotes growth of endothelial cells in vitro. *Lasers Surg Med* 2001;28:355–64.

REPLY

We believe the potential benefits of ultrasound include enhancement of thrombolysis, vasodilation, and increased tissue perfusion. Transcutaneous ultrasound in animals facilitates thrombolysis (1). A pilot trial of transcutaneous low-frequency ultrasound, in combination with tissue-type plasminogen activator (t-PA), has shown feasibility and safety to treat patients with acute myocardial infarction (2).

The study by Miyamoto et al. (3) found that the coronary arteries as well as the coronary veins dilate in response to transthoracic low-frequency ultrasound. Transcutaneous low-frequency ultrasound augments ST-segment elevation resolution in dogs with coronary occlusion treated with t-PA (4). Suchkova et al. (5) found that ultrasound improves tissue perfusion in ischemic limbs, which is associated with capillary dilation. Pretreatment with an inhibitor of nitric oxide synthase blocked ultrasound enhancement of tissue perfusion and capillary dilation. These findings indicate that the effects of ultrasound are mediated through the nitric oxide. Based on this work, it is likely that ultrasound promotes mechanical shear on the endothelial cells and, thus, release of nitric oxide. This thesis is in agreement with that of Drs. Kipshidze.

Robert J. Siegel, MD, FACC
Cedars-Sinai Medical Center
Division of Cardiology
8700 Beverly Boulevard
Room 5335
Los Angeles, CA 90048
E-mail: siegel@cshs.org

Huai Luo, MD
Yochai Birnbaum, MD, FACC
Michael C. Fishbein, MD, FACC
Takashi Miyamoto, MD

doi:10.1016/j.jacc.2004.04.008

REFERENCES

1. Siegel RJ, Atar S, Fishbein MC, et al. Noninvasive, transthoracic, low-frequency ultrasound augments thrombolysis in a canine model of acute myocardial infarction. *Circulation* 2000;101:2026–9.

2. Cohen MG, Tuero E, Blughermann J, et al. Transcutaneous ultrasound facilitated coronary thrombolysis during acute myocardial infarction. *Am J Cardiol* 2003;92:454–7.
3. Miyamoto T, Neuman Y, Luo H, et al. Coronary vasodilation by noninvasive transcutaneous ultrasound. *J Am Coll Cardiol* 2003;41:1623–7.
4. Birnbaum Y, Luo H, Atar S, et al. Noninvasive transthoracic low frequency ultrasound augments thrombolysis in a canine model of acute myocardial infarction—evaluation of the extent of ST-segment resolution. *J Thromb Thrombolysis* 2001;11:229–34.
5. Suchkova VN, Baggs RB, Sahni SK, Francis CW. Ultrasound improves tissue perfusion in ischemic tissue through a nitric oxide dependent mechanism. *Thromb Haemost* 2002;88:865–70.

Transient Ischemic Dilation

Abidov et al. (1) note an increased cardiac event rate in follow-up of patients found to have transient ischemic dilation (TID) as the sole abnormality on stress myocardial perfusion single-photon emission computed tomography (SPECT). However, the finding of severe coronary disease in only a minority (5 of 20) of such patients is in contrast to previous reports (2,3), which conclude TID to be highly specific for severe coronary disease, and it suggests that there are alternate or additional mechanisms to that of balanced diffuse endocardial ischemia due to epicardial coronary stenosis.

Earlier experimental studies have demonstrated a decreased endocardial-to-epicardial flow ratio in response to adenosine (4,5), tachycardia (4), and hypotension (6), particularly in the presence of left ventricular hypertrophy (LVH) and elevated left ventricular end-diastolic pressure (LVEDP) (4–6), as well as coronary stenosis. In addition, redistribution of transmural perfusion would be expected to produce a more pronounced increase in the TID ratio in the presence of LVH, due to a greater subendocardial-to-subepicardial distance. One recent clinical report (7) associates TID, in the absence of focal perfusion defect, with hypertensive LVH.

The possibility that TID may represent a nonspecific marker of stress-induced subendocardial underperfusion by one or more of a number of possible mechanisms and may thus serve as a surrogate of various risk factors for a future cardiac event should be considered. As this phenomenon may not truly be “ischemic” nor represent genuine left ventricular dilation, the term “transient ischemic dilation” may be a misnomer.

Charles J. Hardebeck, MD, FACC
Division of Cardiology
University of Kentucky
210 Thomas More Park
Crestview Hills, KY 41017
E-mail: chardebeck@hotmail.com

doi:10.1016/j.jacc.2004.04.003

REFERENCES

1. Abidov A, Bax JJ, Hayes SW, et al. Transient ischemic dilation ratio of the left ventricle is a significant predictor of future cardiac events in patients with otherwise normal myocardial perfusion SPECT. *J Am Coll Cardiol* 2003;42:1818–25.
2. Weiss AT, Berman DS, Lew AS, et al. Transient ischemic dilation of the left ventricle on stress thallium-201 scintigraphy: a marker of severe and extensive coronary artery disease. *J Am Coll Cardiol* 1987;9:752–9.