partly explain the relatively lower incidence of ischemic heart disease in Southern Europe; however, differences in genotype frequencies most likely cannot explain differences in associations between genotype and risk of ischemic heart disease in different parts of the world. Other possible explanations for such differences exist.

First, the apolipoprotein E polymorphism may act as a susceptibility mutation for ischemic heart disease; such mutations need certain contexts before their impact on risk of disease is expressed. Perhaps a diet rich in saturated fat can explain part of a higher prevalence in cardiovascular disease associated with the epsilon4 allele in Northern Europe compared with Southern Europe.

Second, as the study by Batalla et al. included only 220 patients and 200 controls it is also possible that lack of power in that study explains the negative findings: The power in that study given a two-sided p value <0.05 to exclude the 40% and 60% increases in risk of ischemic heart disease associated with epsilon43 and epsilon44 (as observed in our study), was only 30% and 10%, respectively.

Finally, our observations of increased risk associated with epsilon43 and epsilon44 genotypes could represent chance findings. However, we find this unlikely because 1) epsilon43 and epsilon44 were (in our study and many other studies) also associated with increases in both cholesterol and triglyceride levels, explaining the increased risk of ischemic heart disease, and 2) our observations of increased risk of ischemic heart disease associated with the epsilon4 allele in men agrees with that of a previous meta-analysis including mainly men (4).

Borge G. Nordestgaard, MD, DMSc
Department of Clinical Biochemistry
Herlev University Hospital
DK-2730 Herlev
Denmark
E-mail: brno@herlevhosp.kbh amt.dk

Ruth Frikke-Schmidt, MD
Anne Tybjaerg-Hansen, MD, DMSc

REFERENCES


Dispersion of Repolarization During Induction and Termination of Ventricular Fibrillation

I read with great interest the article by Moubarak et al. (1). The authors found that a high postshock dispersion of repolarization (PSDR) following a T-wave shock is associated with induction of ventricular fibrillation (VF); although following a defibrillating shock, it is associated with its failure and the continuation of VF. However, the authors did not mention anything about the antiarrhythmic drugs (ADs) used by the patients. The drugs were not specified and described in the study. We do not know whether the patients who failed to induce VF with T-wave shock were taking amiodarone. Amiodarone provides homogeneous prolongation of ventricular repolarization (VR) and prevents the development of reentrant circuits. During testing of the implantable cardioverter defibrillator (ICD) it is sometimes very difficult to induce and perpetuate VF with T-wave shock in patients taking amiodarone.

It is well known that different drugs, especially class 1A, class 1C, and class 3 prolong VR in a spatially heterogeneous manner, which results in increased dispersion of VR (2). In a report about propofol, which was used for general anesthesia during ICD testing, it was mentioned that propofol decreased QT interval and dispersion (3).

In light of these findings it is reasonable to suggest that different ADs used by the patients in this study (1) might have caused repolarization changes. We also have no idea about baseline QT measurements. Some patients might have demonstrated high baseline QT dispersions. Hence, patients taking amiodarone or class 1 drugs might show high or low QT intervals and dispersion, which might affect PSDR and inducibility as well as terminability of VF. Thus, without knowing which patient took which drug and baseline QT dispersions, it is not rational to attribute a high PSDR to inducibility or terminability of VF.

Other factors such as disease state, transient ischemia, electrolyte abnormalities, changes in autonomic tone, and hemodynamic stress may also modulate the PSDR and also the success rate of shock attempts. It might be quite helpful to know the PSDR between shock attempts in one patient, because PSDR can be variable between shock attempts in one particular patient or among different patients according to the factors mentioned above. In other words, one can terminate or fail to terminate VF with the same shock strength according to the probability nature of the defibrillation success curve. It would be more reliable to withhold the drugs at least five half-lives before the procedure to minimize the potential effect of drugs on preshock and postshock repolarization times.

Okan Erdogan, MD
Department of Cardiology
School of Medicine
Trakya University
Edirne
Turkey
E-mail: okanerdogan@yahoo.com

REFERENCES


3. Michaloudis D, Fraidakis O, Kanoupakis E, Flossos A, Manios E. Idiopathic prolonged QT interval and QT dispersion: the effects of...

REPLY
The letter by Dr. Erdogan made some good points that, although in our view do not detract from the results and conclusions of our study, are of general interest to the issue of defibrillation success. We appreciate the opportunity to clarify the purpose of our study, which may have eluded some other readers as well.

Most patients in our study were free from antiarrhythmic drugs for five half-lives, except for two patients who had received prior amiodarone therapy that failed to suppress the targeted arrhythmia. Though we do not necessarily subscribe to the value of the 12-lead electrocardiogram as a means to demonstrate the dispersion of repolarization at the myocardial level (1,2), it is quite possible, as Dr. Erdogan states in his letter, that residual amiodarone and other factors such as anesthesia, electrolytes, autonomic tone, etc., may have influenced the dispersion of repolarization in our patients. Any of these influences might enter into the equation that governs the probabilistic nature of the defibrillation threshold (DFT), and that of the fibrillation threshold as well. However, it was not the purpose of our study to discern the effects of such factors on the DFT or ventricular fibrillation (VF) inducibility by ICD shocks.

Instead, our purpose was to show that, in a single patient and at a given time, the probability of inducibility of VF by a T-wave shock and the failure to terminate VF by a second shock were strongly associated with the extent of myocardial repolarization dispersion immediately following the shock (either caused by the shock in case of VF induction, or due to lack of synchronization by the shock in case of VF termination failure). Our intent was directed purely at the mechanistic aspects of VF induction and termination, and to demonstrate and extend for the shock in case of VF induction, or due to lack of synchronization by the shock in case of VF termination failure). Our intent was directed purely at the mechanistic aspects of VF induction and termination, and to demonstrate and extend for the human heart data derived from our earlier experimental studies (3,4), namely, that induction of functional reentry (i.e., VF) is facilitated by dispersion of repolarization with its attendant dispersion of refractoriness. Preshock dispersion is an important ingredient for post-shock dispersion to manifest itself (2), but it was beyond the scope of our study to analyze the multitude of factors that might have influenced the former.

Michael R. Franz, MD, PhD
Cardiology Division
VAMC
50 Irving Street, NW
Washington, DC 20422

REFERENCES
1. Morishige K, Shimokawa H, Yamawaki T, et al. Local adenovirus-mediated transfer of C-type natriuretic peptide (CNP) to porcine coronary arteries, resulting in reduced stenosis of balloon-injured segments. This is an exciting development with obvious therapeutic potential. The investigators suggest several mechanisms by which CNP might regulate vascular remodeling, but they fail to mention the effects of CNP on the vascular renin-angiotensin system. Many studies have demonstrated that the natriuretic peptides have a tonic effect at various sites in the renin-angiotensin-aldosterone cascade (2), and we have demonstrated that CNP inhibits local conversion of angiotensin I to angiotensin II in the human forearm vasculature (3). These vascular effects of CNP in man in vivo are particularly relevant to the therapeutic potential of the technique described by Morishige, because of the known interspecies variability in the effects of the natriuretic peptides (2). The effects of angiotensin II on vascular remodeling are well-documented, and a reduction in local angiotensin II production is a potentially important mechanism for some of the observed effects of CNP.

Neil C. Davidson, MD, MRCP
Department of Cardiology
Westmead Hospital
NSW 2010
Sydney, Australia
E-mail: davidsonneil@bigpond.com

Allan D. Struthers, MD, FRCP

C-Type Natriuretic Peptide and Vascular Remodeling
Morishige et al. (1) have reported local adenovirus-mediated transfer of C-type natriuretic peptide (CNP) to porcine coronary arteries, resulting in reduced stenosis of balloon-injured segments. This is an exciting development with obvious therapeutic potential. The investigators suggest several mechanisms by which CNP might regulate vascular remodeling, but they fail to mention the effects of CNP on the vascular renin-angiotensin system. Many studies have demonstrated that the natriuretic peptides have a tonic effect at various sites in the renin-angiotensin-aldosterone cascade (2), and we have demonstrated that CNP inhibits local conversion of angiotensin I to angiotensin II in the human forearm vasculature (3). These vascular effects of CNP in man in vivo are particularly relevant to the therapeutic potential of the technique described by Morishige, because of the known interspecies variability in the effects of the natriuretic peptides (2). The effects of angiotensin II on vascular remodeling are well-documented, and a reduction in local angiotensin II production is a potentially important mechanism for some of the observed effects of CNP.

Allan D. Struthers, MD, FRCP

REFERENCES

REPLY
We are grateful for the opportunity to respond to the valuable comments by Drs. Davidson and Struthers concerning our recent article in the Journal (1). In our article, we showed that adenovirus-mediated overexpression of C-type natriuretic peptide (CNP) in the porcine coronary artery suppresses vascular constrictive remodeling after balloon injury in vivo. However, as the authors pointed out, we did not mention the possible effect of CNP on the renin-angiotensin-aldosterone system, mainly because we did not specifically examine this system in our study.

It is indeed possible that CNP/cGMP cascade may suppress the vascular remodeling through various mechanisms, including smooth muscle relaxation and inhibition of proliferation and migration of smooth muscle cells and subsequent extracellular


C-Type Natriuretic Peptide and Vascular Remodeling
Morishige et al. (1) have reported local adenovirus-mediated transfer of C-type natriuretic peptide (CNP) to porcine coronary arteries, resulting in reduced stenosis of balloon-injured segments. This is an exciting development with obvious therapeutic potential. The investigators suggest several mechanisms by which CNP might regulate vascular remodeling, but they fail to mention the effects of CNP on the vascular renin-angiotensin system. Many studies have demonstrated that the natriuretic peptides have a tonic effect at various sites in the renin-angiotensin-aldosterone cascade (2), and we have demonstrated that CNP inhibits local conversion of angiotensin I to angiotensin II in the human forearm vasculature (3). These vascular effects of CNP in man in vivo are particularly relevant to the therapeutic potential of the technique described by Morishige, because of the known interspecies variability in the effects of the natriuretic peptides (2). The effects of angiotensin II on vascular remodeling are well-documented, and a reduction in local angiotensin II production is a potentially important mechanism for some of the observed effects of CNP.