Ventricular. Arrythmias In Diabetic Patients With Autonomic Dysfunction

Eun-Jung Park

A. Aim

To elucidate the role of autonomic dysfunction in ventricular arrythmogenesis in diabetic patients and to evaluate methods for detecting those who are susceptible to ventricular tachyarrhythmia and sudden death in this patient population.

B. Background

Large resources are currently being concentrated on the identification of patients at risk of sudden cardiac death. Most sudden death episodes are due to ventricular tachycardia or ventricular fibrillation. The combination of a triggering event and a susceptible myocardium is evolving as a fundamental electrophysiological concept for the mechanism of initiation of potentially lethal arrythmias. Myocardial vulnerability, either structural (infarction, hypertrophy, myopathy, structural electrical abnormality, etc.) or functional (transient ischemia, reperfusion, systemic factors, neurophysiological interactions, toxic effects, etc.), has to be present for triggering events such as frequent and complex PVCs to disorganize patterns of myocardial activation into multiple uncoordinated reentrant pathways.

Among the many causes of increased myocardial vulnerability to ventricular arrythmia, diabetes mellitus is one that has not generally received much recognition that it deserves. In addition to causing coronary heart disease by microangiopathic or endothelial proliferative changes of arterioles, diabetes can cause cardiomyopathy (with both systolic and diastolic dysfunction), chest pain, and, most importantly, arrhythmia independent of coronary disease or hypertension (1).

Interestingly enough, studies since the 1970's have shown that patients with diabetes mellitus who have increased incidence of cardiac arrythmia and sudden death had associated autonomic dysfunction as detected by standard cardiovascular reflex tests even in the absence of clinical coronary artery disease or diabetic cardiomyopathy(2). occasional cardiac autonomic dysfunction may be present before clinical symptoms of generalized autonomic neuropathy are demonstrable. The neuropathy may involve the sympathetic and/or the parasympathetic nervous system. Indeed, it may become so severe as to lead to total cardiac denervation.

The exact mechanism of increased ventricular arrythmia in diabetic patients with cardiac autonomic failure is yet unknown, but we can come up with two likely explanations based on what we know about the-pathophysiology of diabetes mellitus: (a)the presence of subclinical microvascular disease or cardiomyopathy not detectable by current methods available in modern medicine, or (b)the presence of regional sympathetic imbalance in cardiac innervation causing disturbances of repolarization. Studies looking at this issue are relatively lacking in current medical literature.

If microvascular disease causing regional ischemia or silent infarcts is responsible for the observed phenomenon, signal average EKG will be the noninvasive method of choice for detecting delayed and fragmented conduction in the ventricle. Signal averaging is a method that improves signal-to-noise ratio when signals are recurrent and the noise is random. In conjunction with appropriate filtering and other methods of noise reduction, signal averaging can detect late ventricular potentials of I to 25 microvolts, which are waveforms continuous with the QRS complex. These late potentials have been recorded in 70 to 90 percent of patients with sustained and inducible ventricular tachycardia after myocardial infarction, in only 0 to 6 percent of normal volunteers, and in 7 to 15 percent of patients after myocardial infarction who do not have ventricular tachycardia. Late potentials after myocardial infarction have been shown to be an independent risk factor that identifies patients prone to develop ventricular tachycardia. Late potentials also have been recorded in patients with ventricular tachycardia not related to ischemia, such as dilated cardiomyopathies.

Regional variation in ventricular repolarization has been acknowledged to be a risk factor for the development of serious ventricular arrhythmias since the 1980's (3). Differential timing of repolarization between neighboring areas of myocardium provides a potential substrate for ventricular arrhythmias by allowing current eddies and reentrant tachycardia via microcircuits within the ventricle. Nonuniform myocardial repolarization time may result from inhomogeneity of action potential duration or from localized delay in activation, due to slow conduction or altered conduction pathways.

Spatial differences in myocardial repolarization can be assessed by measuring QT dispersion, the interlead variability of QT interval on 12-lead electrocardiogram. Increased QT dispersion has been noted in left ventricular hypertrophy (4), chronic heart failure (5), coronary artery disease (6), and congenital long QT syndrome (7) in association with increased risks for ventricular arrhythmias. Controversy continues to exist, however, in the case of cardiac autonomic failure. Only a limited number of studies have addressed this issue, and the results are conflicting.

Autonomic dysfunction with alterations in vagal and sympathetic innervation can be seen when damage to nerves extrinsic to the heart, such as the stellate ganglia, or to intrinsic cardiac nerves from diseases that may affect nerves primaily (idiopathic autonomic failure or viral infections), or secondarily from diseases that cause cardiac damage. Most recent study looking at QT dispersion in primary autonomic dysfunction didn't.show any statistically significant changes from the control group (8), whereas two other studies in small numbers of patients with autonomic failure due to diabetes mellitus showed increased QT dispersion compared to the controls (9,10).

Why the conflicting results if the resultant pathology is thought to be regional cardiac dysinnervation in both cases? Are there other factors involved? Does diabetic neuropathy affect the heart in a different way from primary autonomic dysfunction? Are the risks of developing ventricular arrhythmia different in the two?

In order to answer these questions, one needs to study the differential ventricular sympathetic innervation in a quantitative way. One method available to date is myocardial radionuclide scintigraphy using 1-123 metaiodobenzylguanidine, a substance taken up specifically by sympathetic nerve terminals. Initially used to visualize pheochromocytoma, radioiodinated mIBG serves as a norepinephrine analogue that is taken up by sympathetic nerve terminals without being metabolized. Therefore, it can be used for the imaging of organs rich in sympathetic innervation, such as the heart, thus allowing for a direct assessment of the integrity of adrenergic myocardial innervation.

The purpose of this study is to investigate, by using aforementioned methods, (a) if there is indeed statistically significant QT dispersion in diabetic patients with autonomic dysfunction in the absence of clinical cardiac disease, (b) if QT dispersion correlates with regional cardiac sympathetic dysinnervation as measured by radionuclide imaging, (c) if QT dispersion can be a reliable predictor of ventricular arrythmia, (d) if there are factors other than regional autonomic failure, such as subclinical ischemic or nonischemic diabetic cardiomyopathy, that might contribute to ventricular arrhythmia in diabetics and (e) if the same questions can be answered in primary autonomic dysfunction when compared to diabetics. Findings of this investigation might shed light to the possible mechanistic role of autonomic dysfunction in ventricular arrythmia and provide guidance for future longterm outcome studies to further probe the issue.

C. Hypothesis

The hypothesis of this prospective analytical survey is the following: cardiac autonomic dysfunction in diabetes mellitus causes ventricular arrythmia via inhomogeneous repolarization due to regional sympathetic denervation.

D. Methods

a. Patient Selection

Subjects will be divided into four groups, each consisting of 50 men and women of all races between ages of 30 and 60:

Group #1--normal controls without autonomic dysfunction

Group #2--normal controls with autonomic dysfunction

Group#3--non-insulin-dependent diabetics without clinical heart disease or autonomic dysfunction

Group #4--non-insulin-dependent diabetics without clinical heart disease but with autonomic dysfunction.

Study groups will be matched by age, sex, race, and body weight. Normal standard 12-lead EKG and transthoracic echocardiogram will be the selection criteria for enrollment Anyone with known cardiac disease such as hypertention (defined as systolic blood pressure >160 and diastolic >110) chest pain syndrome, coronary artery disease, heart failure, conduction system disease, or valvular disease including mitral valve prolapse, history of illicit substance abuse within one year prior to enrollment, and other underlying medical conditions such as chronic renal insufficiency, will be excluded from the study. Subjects will be recruited from CPMC clinic population and staff as well as from the community. Members of the research team will approach potential subjects, explain the study, and obtain informed consent.

E. Study location

The study will take place at the Irving Center for Clinical Research with cardiac imaging studies performed at Nuclear Medicine Laboratory.

Study protocol:

Subject profile data including history of cigarette smoking, alcohol intake, duration of diabetes and treatment mode, and use of other medications, will be obtained upon registration. The research team will be blinded to prior test results and subject profile. Subjects will be admitted to the ICCR and the following procedures will be performed.

Day #1--Measurement of fasting serum glucose and insulin levels, lipid profile, Hgb Aic, electrolytes (Na, K, Ca, Mg, Phos), serum creatinine, as well as urinalysis and urine toxicology. Any electrolyte abnormalities will be corrected.

--Assessment of cardiac autonomic function will be performed with continuous 12-lead EKG and hemodynamic monitoring. Subjects will perform 5 minutes of standardized treadmill excercise followed by 15 minutes of rest, at the end of which they will be asked to do a Valsalva maneuver. Autonomic dysfunction will be defined as having abnormalities in two or more of the following criteria (11):

1. resting heart rate after 15 minutes of rest of 100 beats/min or more.
2. lack of beat-to-beat variability on EKG recording (less than or equal to 10 beats/min).
3. ratio of the longest R-R interval to the shortest of 1.10 or less during Valsalva.
4. ratio of the R-R interval of the 30th beat to 15th after standing of 1 or less.
5. fall in systolic blood pressure of 30 mmHg or more after 1 minute of standing.

--QT dispersion measurement will be performed at the same time subjects are undergoing above test. Mean QT interval of all measurable leads, mean QTc interval, QT dispersion defined as the difference between maximum QT and minimum QT, and QTc dispersion similarly defined, will be obtained from representative 5 second strips from simultaneous 12-lead EKG recordings running at 50mm/sec (twice th normal speed) in three different settings: with excercise, at rest, and with Valsalva maneuver.

Day #2--Serum electrolytes and creatinine level measurement
--Signal average

EKG: Criteria for late potentials will be (1)filtered QRS complex duration >114 to 120 msec, (2)less than 20 microvolts of signal in the last 40 msec of the filtered QRS complex, and (3)the terminal filtered QRS complex signal of less than 40 microvolts for longer than 39 msec.

--24 hour Holter monitoring:

The number of single or complex VPCIs, NSVTIs or sustained VT's will be quantified using the standard computer analysis system. (score 1 for every ten PVC's, 3 for every ten doublets, 5 for every ten triplets, etc.)

Day #3--I-123 mIBG scintigraphy:

Single-photon emission-computed tomography of the heart will be performed with a large field-of-view gamma camera (ZLC 7500, Siemens, Munich, Germany) 15 minutes and 4 hours after the intravenous injection of 111 MBq of 1-123 metaiodobenzylguanidine. Data will be analyzed with computerbased analysis software (SCINTIPAC 7000, Siemens, Munich, Germany). Short-axis, vertical long-axis, and horizontal long-axis slices will be constructed and the left ventricle will be divided into 9 segments. 1-123 mIBG distribution for each segment will be scored by an observer blinded to patient profiles (scores: O=normal, 1=mildly reduced, 2=severely reduced, 3=no activity), and an index of defect will be calculated as summation score per segment. Percent washout rate of 1-123 mIBG will be calculated from the ratio of the index of defect at 15 min post-injection to that at 4 hours post.

F. Analyses

The primary analysis of QT/QTc dispersion and radionuclide washout rate values will involve an analysis of variance in the four study groups. Secondary analysis then will involve post hoc comparison of means followed by correlation of the proven abnormals with the results of 24hour Holter monitoring. The resultant r values (correlation coefficient) will then be compared. In case of QT/QTc dispersion, whether the physiologic state of the subject (excercise, rest or Valsalva) produces any changes in measured values, will also be looked at. For signal average EKG, the results will be analyzed by chi-square test, which will then be compared to the Holter result in the four study groups as well. Possible confounders, such as weight, race, sex, age, cigarrett smoking, alcohol intake, treatment modality (diet control, oral hypoglycemics or insulin), Hgb Alc, fasting plasma glucose and insulin levels, etc. will be also looked at.

G. Significance

This study will compare three different methods of detecting patients at risk of developing fatal ventricular arrythmia: signal average EKG, QT dispersion, and 1-123 mIBG radionuclide imaging. Signal average EKG detects minute delay in ventricular depolarization which might reflect microscopic scarring one might expect to see in diabetes. QT dispersion is a means of detecting spatial repolarization abnormality that might very well be caused by more than one condition, either structural or neuro-hormonal. 1-123 mIBG is a specific way of directly visualizing sympathetic innervation and its integrity.

Finding out abnormalities detected in which of these three test modalities best correlate with increased ectopy observed on Holter monitor, which has been well established as an independent marker for predicting ventricular arrythmias and sudden death, and which study subgroup shows the strongest correlation, might shed light to many of the questions that have been raised.

Does autonomic dysfunction play a role in triggering arrythmia in only diabetics but not in primary autonomic dysfunction? Can QT dispersion be completely attributed to regional cardiac dysinnervation, or are there other factors involved? How does QT dispersion compare with signal average EKG in predicting ventricular arrythmia? Can we risk-stratify diabetic patients by combining the two methods? What is the longterm survival outcome of this patient population, and would prophylactic antiarrythmic therapy be warranted? This study might be able to provide valuable guidance for future investigations that will specifically address these issues.

H. References

1 Regan TJ, et al. Diabetic cardiomyopathy: experimental and clinical observations. NEW JERSEY MEDICINE 1994 Nov. 91(11):776-8.
2 Zoneraich, S. DIABETES AND THE HEART Springfield, Ill. Charles C. Thomas, Publisher, 1978. p.303
3 Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. CIRCULATION 1983; 67:1356-1367.
4 Perkiomaki JS, et.al. Dispersion of the QT interval and autonomic modulation of heart rate in hypertensive men with and without left ventricular hypertrophy. HYPERTENSION 1996 Jul. 28(l):16-21.
5 Fei L, et.al. QT dispersion and RR variations on 12-lead ECGs in patients with congestive heart failure secondary to idiopathic dilated cardiomyopathy. EUROPEAN HEART JOURNAL 1996 Feb. 17(2):165-6.
6 Bogun F, et.al. QT dispersion in nonsustained ventricular tachycardia and coronary artery disease. AMERICAN JOURNAL OF CARDIOLOGY 1996 Feb. 77(4):256-9.
7 Priori SG, et.al. Dispersion of the QT interval. A marker of therapeutic efficacy in the idiopathic long QT syndrome. CIRCULATION 1994 Apr. 89(4):1681-9.
8 Lo SS, Mathias CJ, Sutton MS. QT interval and dispersion in primary autonomic failure. HEART 1996 May. 75(5):498501.
9 Wei K, et.al. Association between QT dispersion and autonomic dysfunction in patients with diabetes mellitus. JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY 1995 Oct. 26 (4) :859-63.
10 Kirvela M, Yli-Hankala A, Lindgren L. QT dispersion and autonomic function in diabetic and non-diabetic patients with renal failure. BRITISH JOURNAL OF ANAESTHESIA 1994 Dec* 73(6):801-4.
11 Roy TM, Peterson HR, Snider HL, et al. Autonomic influence on cardiovascular performance in diabetic subjects. AMERICAN JOURNAL OF MEDICINE 1989 87:382