Exercise Test–Induced Arrhythmias

James Beckerman, Teresa Wu, Sarah Jones, and Victor F. Froelicher

Exercise testing is commonly used by clinicians to characterize cardiovascular risk by detecting myocardial ischemia and assessing response to exercise. However, a consensus has not previously existed regarding the significance of exercise test-induced arrhythmias due to conflicting results from the available studies. Recent studies with longer follow-up and improved technology have therefore stimulated this current review of the topic. Despite the continued debate in the literature regarding the prognosis of ETIA in a general population, there is sufficient evidence to suggest that clinicians should closely evaluate and follow those patients with arrhythmias during exercise testing and aggressively modify risk factors for coronary artery disease.
Published by Elsevier Inc.

Exercise testing is frequently used by clinicians as a noninvasive assessment of myocardial ischemia that along with patient history and physical examination helps characterize cardiovascular risk. In addition, exercise testing can be used to identify cardiac arrhythmias, particularly those brought on by exercise.[1,2] The useful information acquired can complement information obtained from ambulatory monitoring and electrophysiologic testing. A consensus has not existed regarding exercise test–induced arrhythmias (ETIA) because of the conflicting results from the available studies. However, recent studies with longer follow-up and improved technology provide motivation to review the literature to see if consensus is now possible. The purpose of this review is to explore the basis of ETIA, characterize their prevalence, and review the literature investigating their prognosis. The majority of the article is devoted to exercise test–induced ventricular arrhythmias (ETIVA) rather than exercise test–induced supraventricular arrhythmias (ETISVA) because ETIVA have more published studies. We have performed a systematic review using PubMed (keywords: exercise test, arrhythmias, and prognosis) as well as scanning the citations in articles gathered manually. The main results from this process are the 22 studies summarized in Table 1 using critical features that help to qualify their results and to find common points for consensus.

Background

Exercise produces a number of important physiological changes which may precipitate cardiac arrhythmias, including the activation of the sympathetic nervous system and an increase in the availability of circulating catecholamines.[3-5] This may result in increased automaticity, enhanced triggered activity, and premature beats leading to activation of reentrant circuits. Atrial arrhythmias may also reflect underlying left atrial enlargement, mitral regurgitation, and ventricular dysfunction. Other potential proarrhythmic mechanisms include electrolyte shifts, baroreceptor activation, myocardial stretch, and ischemia.[6,7] Spontaneous genetic mutations as well as familial genetic disorders may also predispose individuals to ETIA.

Whereas hypokalemia has been implicated in polymorphic ventricular tachycardia and hyperkalemia can lead to either bradycardia or ventricular tachycardia, changes in serum potassium levels that normally occur with exercise are actually well tolerated. Vigorous exercise can double potassium levels, decrease pH, and raise catecholamines more than 10-fold. If any of these changes are experienced at rest, there is an

From the Division of Cardiovascular Medicine, Stanford University Medical Center and Veterans Affairs Health Care System, Palo Alto, CA.

Address reprint requests to Victor Froelicher, MD, VA Palo Alto Health Care System, 3801 Miranda Avenue, 111C, Palo Alto, CA 94304. E-mail: vicmd@aol.com

0033-0620/$ - see front matter
Published by Elsevier Inc.
doi:10.1016/j.pcad.2005.02.011

Table 1. Summary of the Key Features of the Studies of Exercise Test–Induced Ventricular Arrythmias

Study	Year	Sample Size	Population	Age (y)	Sex (% Female)	Exercise Test	Method	Definition
Clinical population, PVC studies								
Parlington et al, *Am Heart J*, Beckerman, ANIE, LB and PA VAHCS	2003	6213	Patients referred for clinical reasons	59 ± 11	0	Symptom-limited ramp treadmill	All tests coded by MDs/RNP during test, over read by authors	Frequent PVCs = >10% of QRS complexes during any 30 s, or ≥3 consecutive PVCs during exercise or recovery
Frolkis et al, *NEJM*, Cleveland Clinic	2003	29 244	Referred patients without heart failure, valve disease, or arrhythmia	56 ± 11	30	Symptom-limited treadmill	ECG images and arrhythmias "prospectively recorded"	Frequent = ≥7 PVCs/min, bi/trigeminy, couplets/triplets, VT/VF. Classified according to Lown
Elhendy et al, *Am J Cardiol*, Mayo Clinic, Rochester, Minn	2002	1460	Patients with intermediate pretest probability of CAD, no hx MI/CABG, no arrhythmia hx	64 ± 10	41	Symptom-limited treadmill, Bruce protocol in 91%, more gradual protocol in remainder	ECG	Classified as complex (couplets, bi/trigeminy, or multiform), frequent (>5 PVCs/min), NSVT (≥3 PVCs during episodes <30 s), VT, or VF
Schweikert et al, *Am J Cardiol*, Cleveland Clinic Foundation	1999	2743 with perfusion scan, 424 with coronary angio	Adults without heart failure or known PVCs at rest; no hx invasive cardiac procedures	62 ± 10	30	Symptom-limited Bruce protocol treadmill	ST segments collected and entered online	Significant ETIVA = frequent or complex ventricular activity (>7 PVCs/min, couplets, triplets, bi/trigeminy), NSVT = ≥3 PVCs of <30 s duration, or VT or VF
Casella et al, *Int J Cardiol*, Ospedale Maggiore, Bologna, Italy	1993	777	Consecutive stable out-patients 1 year post–Q-wave MI	57 ± 9	9	Symptom-limited Bruce protocol treadmill	12-Lead ECG continuously monitored	Any PVC, not detected at rest but observed during exercise, categorized into simple (≤2 Lown) vs complex (≥3 Lown) ETIVA
Marieb et al, *Am J Cardiol*, University of Virginia School of Medicine	1990	383	Patients with chest pain, cath and perfusion scan	58 ± 10	15	Symptom-limited exercise test	12-Lead ECG continuously monitored, technicians recorded arrhythmias detected on monitor	Any PVCs not noted at rest, but observed during exercise or recovery; classified as rare (<5) or frequent (>5), multiform PVCs, couplets, VT (≥3 PVCs), and VF
Nair, et al, *Am J Cardiol*, Creighton University School of Medicine, Nebraska	1984	186	Patients with CAD by coronary angio (excluding CHF, PVCs, other ECG abnormalities); many had MI	59 ± 9	16	Symptom-limited Bruce protocol treadmill	12-Lead ECG recorded and continuously monitored during and for ≥6 min after exercise	Complex ETIVA = pairs or runs, multiform, or ≥ 10/min

Rest/Pretest PVCs or Arrhythmias Considered?*	Hx Arrhythmias Considered?	Categorization†	Prevalence	End Points	Follow-up (y)	Risk or Hazard	More ETIVA with Ischemia/ ST Depression?	Conclusion
Not excluded, considered	Not excluded, ignored	During exercise or recovery	8% (n = 503)	All-cause mortality (1256 total deaths, 550 CV deaths, CV mortality in later paper)	6 ± 4	HR = 2	Yes (patients with ETIVA with higher prevalence EI ischemia)	Rest/ETIVA both predict CV mortality; EI ischemia, no affect on prognostic value of ETIVA/ arrhythmic substrate does; ETIVA predict mortality in those with/without disease
Excluded	Excluded	During each stage of exercise, during recovery, during exercise and recovery	3% (2% during recovery, 2% exercise and recovery)	All-cause mortality (1862 deaths)	5.3	HR = 1.5 during recovery	Yes (higher prevalence ischemia for those with recovery PVCs)	ETIVA in recovery but not exercise associated with increased risk of death
Not excluded, ignored	Excluded	At rest, during exercise, or recovery	10% (n = 146)	Cardiac death and nonfatal MI (36 patients)	2.7	2.5 × (1-6)	Yes	ETIVA predict cardiac death/ nonfatal MI in suspected CAD; independent predictors of cardiac events were ETIVA and MaxHR
Excluded, ignored	Severe cases excluded	During exercise, final stages of exercise	5% (n = 128), 10% (n = 42 angio cohort)	All-cause mortality	2	HR = 0 (for short-term mortality)	No	ETIVA associated with perfusion defects but not angiographic severity/short-term mortality
Not excluded, ignored	Not excluded, ignored	At rest, during exercise and recovery	29% (n = 228)	All-cause mortality (24 deaths, 5 had ETIVA)	2	RR = 0	No	In patients with coronary disease or MI, ETIVA w/o prognostic power
Not excluded, ignored	Not excluded, ignored	At rest, each minute of exercise, and 1, 2, 3, and 5 min after exercise	42% (n = 162)	CV death (41 deaths), 9 Mis, 39 CABG	4-8	2× risk univariately (weakly significant in Cox model)	Yes (patients with ETIVA more likely to have ST-segment depression)	ETIVA predicted CV death/events; ETIVA patients did not differ (MI, perfusion defects, EF, diseased vessels); ETIVA more likely with EI ischemia
Excluded, ignored	Excluded	Supine and standing, end each 3-min exercise stage, max and each minute recovery	2% (n = 3)	CV death (8 deaths) and sudden death (4 deaths)	4 ± 1	RR = 0	Ignored	ETIVA did not predict sudden death or 4-year mortality in patients with CAD

(*continued on next page*)

Table 1 continued.

Study	Year	Sample Size	Population	Age (y)	Sex (% Female)	Exercise Test	Method	Definition
Clinical population, PVC studies								
Nair, et al, *J Am Coll Cardiol*, Creighton University School of Medicine, Nebraska	1983	280	Patients referred for chest pain, no MI or PVCs at rest	55 ± 9 (men) and 53 ± 9 (women)	30	Bruce protocol treadmill	12-Lead ECG continuously monitored during and for ≥6 min after exercise; all PVCs recorded and counted	Complex ETIVA = pairs or runs, multiform, or frequency, >10/min
Califf, et al, *JACC*, Duke University Medical Center	1983	1293	Medically treated patients with cardiac cath; if evaluated for VAs or CHF excluded; 620 patients had CAD	48	?	Treadmill	Samples of each arrhythmia recorded on ≥4 leads of 12-lead ECG	Simple VAs = ≥1 PVC; VAs further categorized into paired complexes (2 consecutive PVCs) and VT (≥3 PVCs)
Sami, et al, *Am J Cardiol*, Stanford University, Montreal Heart Institute, Mayo Clinic, University of Washington	1984	1486	Coronary Artery Surgery Study registry with angiographic CAD	50 ± 10	20	Bruce protocol	12-Lead ECG continuously monitored	ETIVA = PVCs during exercise or recovery, provided a 3-min control, pre-exercise test showed no PVCs
Weiner et al, *Am J Cardiol*, Boston University Medical Center	1984	446 (group 1 with arrhythmias and group 2 without)	Consecutive series of patients with cath	53 ± 7	22	Bruce protocol graded treadmill	12-Lead ECG continuously monitored on a 3-channel oscilloscope; all PVCs recorded	Complex PVCs = pairs or runs, multiform, or >20 bpm
Udall et al, *Circulation*, Long Beach and UCI Medical Center	1977	6500	Patients referred for clinical reasons	?	20	Ellestad max protocol treadmill	ECG	"Ominous" PVCs = multiform, bigeminal, repetitive and VT
Clinical population, patients with heart failure								
O'Neill, *JACC*, Cleveland Clinic	2004	2123	left ventricular EF ≤35%	54 ± 11	20	Symptom-limited cardiopulmonary treadmill testing	Systematic ECG data during rest, exercise and recovery	Severe PVCs = ventricular triplets, sustained/ nonsustained VT, ventricular flutter, polymorphic VT or VF

Rest/Pretest PVCs or Arrhythmias Considered?*	Hx Arrhythmias Considered?	Categorization†	Prevalence	End Points	Follow-up (y)	Risk or Hazard	More ETIVA with Ischemia/ ST Depression?	Conclusion
Excluded	Excluded	Supine and standing, end each 3-min exercise stage, max and each minute recovery	27% (n = 76)	Coronary events (1 CABG and ETIVA, 6 w/o CABG with ETIVA, 5 with CABG w/o ETIVA, and 12 w/o ETIVA or CABG	4 ± 2	1.25× risk for those with ETIVA or surgery, no increased risk for those with both surgery and ETIVA	Ignored	ETIVAs has lower predictive value for significant CAD than ST-segment depression; ETIVA site of origin not helpful
Not excluded, considered	Excluded	2 min pre, during, and for 8 min after testing	23% prevalence in CAD patients, 7 % in those with normal coronary arteries	CV death	3	2.5× for severe, 1.7× for simple	Ignored	Higher prevalence of CAD, left ventricular dysfunction in patients with paired complexes and VT
Not excluded, ignored	Not excluded, ignored	At rest, every 3 min during exercise, at peak, and each minute recovery	10%	Death from any cause, cardiac death, and cardiac event	4.3	RR = 0	Ignored	Only the number of coronary arteries diseased and the EF were associated with cardiac events
Not excluded, considered (5% with rest PVCs)	Not excluded, ignored	At rest, during exercise, during recovery	19% (30% in the 120 patients with 3-vessel/LM CAD)	Total cardiac mortality (6 deaths in group 1 and 23 in group 2)	5.3	1.4×	Yes (patients with ETIVA more likely to have severe ischemia	In asymptomatic persons w/o CAD, ETIVAs not predictive; ETIVA associated with exercise-induced ischemia, but not increased cardiac mortality
Not excluded, considered	Not excluded ignored	At rest, during exercise (increased/ decreased PVCs during exercise), during recovery	20 % (n = 1327)	Coronary events (MI, angina, or cardiac death)	5	3.8× for PVCs alone, 6.7× for ischemic ST changes and PVCs	Not mentioned	PVCs suggested heart disease when they increased with exercise; patients with PVCs plus ischemic ST changes had higher risk coronary events those with either alone
Considered	Considered	Rest, exercise and recovery	140 (7%) had severe ventricular ectopy during recovery	All-cause mortality, with censoring for interval cardiac transplantation	3 y	Severe PVCs during recovery with adjusted HR 1.5	Not mentioned	After adjustment for PVCs at rest and during exercise, $\dot{V}O_2$ max, and other potential confounders, severe PVCs during recovery remained predictive of death (adjusted HR 1.5), whereas those during exercise not predictive

(*continued on next page*)

Table 1 continued.

Study	Year	Sample Size	Population	Age (y)	Sex (% Female)	Exercise Test	Method	Definition
Healthy population, PVC studies								
Morshedi-Meibodi, et al, *Circulation*, Framingham Heart Study	2004	2885	Healthy individuals screened to exclude heart disease (n = 542)	43 ± 10	52	Symptom-limited/submax bike/treadmill	Digital computer system used, arrhythmias identified by technician and verified by cardiologist	ETIVA = PVCs/min of exercise (mean = 0.22/min exercise), frequent ETIVA = above the median
Jouven, et al, *NEJM*, Paris Prospective Study	2000	6101	Asymptomatic men without CVD employed by the Paris Civil Service	42-53	0	Bicycle (>3 successive workloads and max duration of 10 min)	ECG continuously monitored	Frequent PVCs = ≥2 PVCs, making up >10 % of all ventricular depolarizations on any 30 s ECG
Busby, et al, *J Am Coll* Cardiol Baltimore, Maryland	1989	1160	Asymptomatic volunteer participants screened for cardiac disease	21-96	35	Symptom-limited max Balke treadmill (done an average of 2.4×)	ECGs; aVF, V_1, and V_4 continuously monitored by oscilloscope and audible cardiotachometer; analog recordings for playback	Complex ETIVA = frequent or repetitive PVCs, frequent = ≥10% of the bpm, and repetitive = salvos of ≥3 at ≥100 bpm; complex ETIVA characterized by their time of first occurrence
Froelicher et al, *Am J Cardiol*, USAFSAM	1974	1390	USAF aircrew men referred for evaluation	38 (20-54)	0	Symptom-limited Balke protocol treadmill	Continuous ECG strips reviewed on microfilm	Ominous ETIVA = frequent PVCs at/near max or 3 consecutive PVCs/VT any time, frequent PVCs = ≥10 PVCs out of any 50 beats with other PVCs that increased with exercise or 3 in a row
VT studies								
Tamakoshi et al, *J Cardiol*, Cardiovascular Institute Hospital Tokyo	2002	25 075	Healthy patients without hx PVC/VT	53 ± 9	44	Max bicycle/treadmill	Reviewed	NSVT = ≥8 PVCs at >100 bpm

Rest/Pretest PVCs or Arrhythmias Considered?*	Hx Arrhythmias Considered?	Categorization†	Prevalence	End Points	Follow-up (y)	Risk or Hazard	More ETIVA with Ischemia/ ST Depression?	Conclusion
Not excluded, ignored	Excluded	During each stage of exercise (submax up to 85% age predicted) and during recovery	27% (n = 792)	CV events (142 events [MI, ACS, CV death]), all-cause mortality (171 deaths)	15	Greater than 2× adjusted risk for all-cause mortality but not CV end points	No	ETIVA were associated with increased risk of death (but not CV events or ischemic ST-segment response) at much lower threshold than previously reported
Not excluded, considered	Polymorphic PVCs excluded	Before exercise, during exercise, and during recovery	6% (0.8% before exercise, 2.3% during exercise, 2.9% during recovery)	Death from CV, fatal MI, sudden death	23	RR = 2.7 (1.8-4.0)	Not clarified	ETIVA during exercise associated with risk of CV death, but frequent PVCs before exercise and infrequent PVCs were not, ETIVA during recovery associated with non-CV death; risk similar to ST depression
Not excluded, considered (9/40 had resting PVCs)	Excluded (major abnormalities)	Before exercise (supine, sitting, and after HV and standing), during exercise, ≥6 min into recovery	7% (frequent or repetitive PVCs)	All-cause death and cardiac events	6 ± 3	RR = 0	No	ETIVA did not predict increased cardiac morbidity/ mortality and not associated with EI ischemia; ETIVA increased with age
Not excluded, ignored	Not excluded, ignored	During the control period (supine and standing), during and after exercise	2% with ominous ETIVA	Angina, MI, CV death	6.3	3×	Not mentioned	ETIVA had a low predictive value for CV events but significant risk
Not excluded, ignored	Excluded	During exercise and recovery		0.08% angiographic findings (6 patients had ischemia, 2 had cardiomyop-athy, 5 had other CV disease)	No follow-up; cross-sectional retro-spective study	VT more common in cardiomyop-athy		VT at elevated HR 12 of the 20 patients

(*continued on next page*)

Table 1 continued.

Study	Year	Sample Size	Population	Age (y)	Sex (% Female)	Exercise Test	Method	Definition
VT studies								
Yang, et al, *Arch Intern Med*, LBVAHCS	1991	3351	Veterans	60 ± 9 (21-88)	3	Symptom-limited Balke treadmill	3 Leads (II, V_2, V_5) continuously monitored during exercise; recorder automatically printed out any ectopic beats	NSVT = ≥3 consecutive PVCs, VT = >30 s or requiring intervention
Fleg et al, *Am J Cardiol*, Baltimore	1984	922	Healthy volunteers without evidence of CAD	54 ± 16 (21-96)	35.2	Modified Balke max treadmill	Leads I, aVF, V_5 screen and audibly monitored/FM tape storage; 12-lead ECG last 15 s each exercise stage	VT = ≥3 consecutive PVCs at >100 bpm
Detry et al, Catholic Hosp Brussels, Belgium	1981	7500	Patients referred for clinical reasons	?	?	Max symptom-limited bicycle (20 W and increased 20 W every min)	ECG	VT = ≥4 consecutive PVCs (sustained VT = >20 consecutive beats or recurring VT; single short-run VT = 4-12 consecutive PVCs)
Codini et al, *Cathet Cardiovasc Diagn*	1981	5730 (47 had VT and composed the study group)	Consecutive patients, 40 with heart disease	57 ± 11 (32-76)	13	Bruce or modified Bruce protocol treadmill	12-Lead ECG screen monitored; 24 patients Holtered	VT defined as a run of ≥3 PVCs in a row

*Rest/Pretest PVCs refer to those PVCs/arrhythmias recorded directly prior to exercise testing. Hx arrythmias refer to a medical history of resting PVCs or arrythmias. "Not excluded" indicates that a study ignores (does not mention) Rest/Pretest PVCs or Hx arrythmias, or considered them in the analysis.

†Categorization refers to the time periods into which ECG recording was classified.

increased risk of arrhythmia and cardiac arrest, yet in exercise they are usually well tolerated.[8] It has been postulated that the heart may be protected from exercise-induced chemical stress by an anti-arrhythmic interaction among these chemical changes. Catecholamines may offset the harmful cardiac effects of hyperkalemia and acidosis and improve action-potential characteristics in potassium-depolarized ventricular myocytes. This could result from an increase in the inward calcium current modulated by both adrenergic and nonadrenergic hormones.

Generally, hyperkalemia decreases the incidence of norepinephrine-induced arrhythmias. The efficacy of the mutual antagonism is reduced when the combination of acidosis, hyperkalemia, and high levels of norepinephrine are superimposed on a heart with regional ischemia or a small infarct. In addition, the heart may be at greatest risk in the postexercise period when plasma potassium is low and the adrenergic tone is high. Most dangerous exercise-induced arrhythmias occur at this time and they can be lessened or avoided by cool-down activities. Abnormal regulation of electrolyte and cardiac sympathovagal balance in recovery most likely increases the susceptibility to arrhythmias, particularly when ischemia is present.

Any alteration in the delicate chemical balance and natural physiological response to exercise may also contribute to cardiac arrhythmias. Recent studies have linked certain anti-arrhythmic drugs with ETIVA.[9-12] Ranger et al[13] hypothesized that sinus tachycardia during exercise may enhance flecainide-induced conduction slowing by increasing use-dependent sodium channel blockade, thereby facilitating the occurrence of ventricular reentry. Their study found

Rest/Pretest PVCs or Arrhythmias Considered?*	Hx Arrhythmias Considered?	Categorization†	Prevalence	End Points	Follow-up (y)	Risk or Hazard	More ETIVA with Ischemia/ ST Depression?	Conclusion
Not excluded, ignored	Not excluded, considered (reason for exercise test)	During exercise and recovery	1% with 7 % reproducible; sustained VT = 5/55 patients	Death from CV (1 death), sudden death (1 death)	2	RR = 0	Yes	Ischemia is more likely with ETIVT, but ETIVT does not increase risk of mortality
Not excluded, ignored	Not excluded, ignored	At rest, during exercise and recovery (2, 4, and 6 min after exercise)	1.10%	Symptoms of heart disease (0 events), syncope or sudden death (0 events)	2	RR = 0	No (those with VT w/o increased prevalence of ischemic response)	Asymptomatic nonsustained VT at peak exercise w/o risk
Not excluded (26 patients had PVCs at rest, 6 had hx VT), considered	Not excluded, ignored	During exercise	0.6 % (40 with VT/6 with VF)	Cardiac death (10 sudden deaths and 1 operative death, 91 % had CAD)	2.6	No risk for short-run VT, 3.6× risk for sustained VT or VF	Yes (SVT and VF associated with ST depression)	Sustained ETIVT is associated with poor prognosis compared to short-run VT
Not excluded, considered (resting PVCs in 10 patients)	Not excluded, ignored	At rest, during exercise, during 10 min recovery, during exercise and recovery	0.08%	Cardiac disease	no FU	No FU	Yes (44/47 with VT had ischemic ST changes)	ETIVT rare in patients with heart disease older than 45 years

that the best predictor of increasing QRS duration was the change in QRS duration produced by flecainide at rest.

Other studies have delineated varying electrical patterns that may predispose patients to ETIVA. Tuininga et al[14] studied the initiating mechanisms of ETIVA in 6000 patients. One percent had 194 episodes of ventricular tachycardia during the test. Forty-two percent of these events occurred during exercise and 58% during recovery. Two different initiating patterns were observed before ventricular tachycardia: a short-long-short sequence of R-R intervals (28%) or a regular R-R pattern (63%).

In addition to a regular R-R pattern, one of the forms of the long QT syndrome has also been linked to exercise-induced sudden death.[15] The gene *KCNQ1* (formerly called *KVLQT1*) is a Shaker-like voltage-gated potassium channel gene responsible for the LQT1 subtype of LQTS (long QT syndrome). In general, heterozygous mutations in *KCNQ1* cause Romano-Ward syndrome (LQT1 only), whereas homozygous mutations cause Jervell and Lange-Nielsen syndrome (LQT1 and deafness). The majority of these mutations are missense mutations. However, other types of mutations, such as deletions, frame shifts, and splice-donor errors have also been reported. The combination of normal and mutant *KCNQ1* α-subunits has been found to form abnormal IKS channels; hence, mutations associated with the *KCNQ1* gene are also believed to act mainly through a dominant-negative mechanism or loss-of-function mechanism.[16]

Paavonen et al[17] studied the effects of mental and physical stress on patients with LQTS. During exercise, the corresponding QT adaptation to exercise stress was more pronounced in

healthy controls (−47 milliseconds) than in LQT1 (−38 milliseconds) or LQT2 patients (−38 milliseconds). During exercise, changes in serum potassium concentrations were correlated to changes in QT intervals in controls, but not in patients with LQTS.

Familial catecholaminergic polymorphic ventricular tachycardia is a rare arrhythmogenic disease manifesting with ETIVA or stress-induced ventricular arrhythmias, syncope, and even sudden death. Catecholaminergic polymorphic ventricular tachycardia is inherited as an autosomal dominant or autosomal recessive trait, usually with high penetrance.[18] The clinical, structural, and electrocardiographic findings in this disorder have been characterized by use of genome-wide linkage analysis, mapping the disease-causing gene to chromosome 1q42 to q43. Mutations of the cardiac ryanodine receptor gene (*RyR2*) have been demonstrated to underlie this life-threatening disease. In addition, *RyR2* mutations were identified in patients affected with a variant form of arrhythmogenic right ventricular dysplasia (ARVD2), a phenotypically distinct disease entity. Identification of the causal mutations has enabled molecular diagnosis in the affected families, which is of major importance in identifying individuals at risk for an arrhythmia. Recently, several groups have delineated the functional effects of the *RyR2* mutations associated with catecholaminergic polymorphic ventricular tachycardia and ARVD2. The results are slightly contradictory, and further studies are thus needed to clarify the exact molecular mechanisms leading to arrhythmia induction.

Methodologies of Clinical Studies

The headings in Table 1 address the important methodological issues and require some explanation in varying degree of intensity. The studies are organized from newest to oldest but our only caveat regarding this order is that "newest is not always the best." The exercise used may have a bearing particularly if submaximal exercise was applied or if modalities and rate of workload differed but we could not find any tendencies for these factors to explain differences across studies. We tried to assess if the researchers considered the presence of rest premature ventricular contractions (PVCs) or other arrhythmias immediately before the test or in the patient's medical history. But it was hard to come to conclusions regarding the impact of these important factors because of the inconsistencies of reporting in the articles. The "arrhythmic substrate" may have as much a bearing on prognosis as the ETIA themselves. Characterization of the timing of the arrhythmias is also sorely incomplete. Basic information such as whether PVCs are suppressed or increased by exercise is usually not available in the studies. Therefore, we cannot provide a consensus on the meaning of these potentially important patterns. Other factors with greater description provided in the articles will be dealt with below.

Definition of ETIVA

Study design and the means by which ETIA have been captured have differed significantly enough that it has been difficult to come to a consensus regarding prevalence rates, much less extrapolating prognostic information from data available. Clearly, the methods of recording and capturing PVCs greatly affect the prevalence data and as technology advances, the multitude of options available for data collection may make standardization even more difficult. Even in studies where data have been obtained using similar equipment configurations, there have been inconsistencies in categorizing and defining the information acquired. These inconsistencies often stem from basic controversy in deciding what data should be labeled as an ETIVA. This inconsistency in the definition of ETIA has played a large role in limiting not only data collection, but also the prognostic value of much of the information available. Studies have used varying criteria to define ETIA. Some studies define ETIA to be present if any premature atrial or ventricular complex was recorded during exercise, whereas others require more significant or sustained ectopy. Some have defined supraventricular or ventricular tachycardia to mean 3 consecutive beats, whereas others require longer runs. Another approach has been to consider a certain threshold of complexes per minute or an absolute number of ectopy per minute.

The prevalence of ETIVA has been shown to be more reproducible on future exercise tests if

frequent or complex PVCs are used as markers for ETIVA as compared with occasional PVCs.[19] In addition, others have documented an increased risk of mortality in those with frequent or complex PVCs during exercise compared to those with only occasional PVCs.[20,21]

The problems with defining ETIVA do not lie solely in differentiating how many PVCs are witnessed during exercise, but also include issues demarcating the exact time frame by which a ventricular arrhythmia is considered to be exercise-induced. In addition to examining ventricular arrhythmias during the actual exercise period, data concerning arrhythmias before the test and during recovery should be considered. Furthermore, whether one does a cool-down walk after exercise can affect the appearance of ectopy. To complicate things further, data have also been extrapolated from studies examining the prognostic importance of resting PVCs immediately before testing (ie, the arrhythmic substrate).

Detection of ETIVA

Many different technologies have been used to record and diagnose arrhythmias occurring in association with exercise testing. The earliest studies simply relied on physicians and/or technicians to recognize arrhythmias appearing on the monitor and/or recorded on the electrocardiogram (ECG) output. This was dependent upon the skill and attention of the observer to note the arrhythmia and record it by manually initiating an ECG recording. As the exercise devices became more sophisticated, they incorporated software algorithms that detected arrhythmias and automatically initiated an ECG recording. The noise associated with exercise has represented a challenge to these algorithms, frequently triggering them. Therefore, in most clinical settings they are disabled.

Because of the exercise environment, algorithms developed for monitoring patients in the hospital or during ambulatory ECG recordings cannot easily be implemented or relied upon. Some commercially available exercise systems use total disclosure of all ECG complexes. Noise can make the recognition of arrhythmias difficult even using these types of printouts. More recently, exercise systems have included the capacity to record all ECG data during and after exercise. These stored, digitized signals can be subjected to sophisticated software techniques offline using noise reduction algorithms and Holter-like ECG analysis.

Study Design

Population Selection

Multiple factors have been shown to be associated with the prevalence of ETIVA. The problem lies in elucidating the exact relationship between these factors and ETIVA and explaining their prognostic significance. In the past, many studies attempted to clarify the relationship between ETIVA and factors such as age, sex, arrhythmic substrate, and presence of cardiac disease, but conflicts remain. Analysis of these studies suggests that the inconsistencies between them may be secondary to differences in patient selection, data stratification, and study design.

Some studies have focused on particularly healthy populations such as aviators and police officers, whereas others have targeted random samples with or without screening for baseline heart disease (ie, Framingham Heart Study). Other studies have targeted patients referred for exercise testing for clinical reasons, including those known to have arrhythmias. Different prevalences of ETIVA can be expected from these different populations.

Age

Many studies have demonstrated a direct relationship between age and the prevalence of ETIVA. Fleg and Lakatta[22] assessed the prevalence of ETIVA in 597 male and 325 female healthy volunteers between 21 and 96 years of age. Of the 1.1% with identifiable exercise-induced arrhythmias, only 1 was younger than 65 years. In other studies, the incidence of ETIVA and increasing age was not shown to be congruent. During serial maximal treadmill testing on 543 male volunteers, the prevalence of ETIVA was 30% to 36% in men aged 25 to 34 years, 32% to 38% in those aged 35 to 44 years, and 36% to 42% in those aged 45 to 54 years. These differences were not statistically significant.[23] However, the USAF School of Aerospace Medicine (USAFSAM)

Table 2. Number and Percentage of Subjects With PVCs Other Than Single or Occasional

Age (y)	n	%
20-29	24	6.6
30-39	52	7.6
40-53	78	13.1

Froelicher et al, AGARD Study; n = 1640 healthy aviators.

findings clearly support the age relationship to ETIVA (Tables 2 and 3). Furthermore, it is critical to categorize data into age-specific subsets to determine if ETIVA at a younger age carries more prognostic significance than in the elderly. Aging itself, alterations in sympathetic tone, or the diseases that accrue with aging may contribute to varying age-related prognosis.

Ischemia

In addition to stratifying the patient population based on age, studies have also examined ETIVA as it relates to a patient's risk for myocardial ischemia as well as the presence of heart disease. Because arrhythmias are a part of acute coronary occlusion and acute coronary syndromes, particularly myocardial infarction (MI), it seems reasonable to expect this association during exercise. Some studies have suggested an association of ETIVA with exercise-induced ischemia.[22,24] However, other studies refute these results.[25-29] It does seem apparent that ETIVA are more common in patients with coronary artery disease (CAD).

For example, Elhendy et al[30] evaluated the relationship between ETIVA and myocardial wall motion abnormalities during exercise echocardiography. The study included 1460 patients with intermediate pretest probability of CAD. Exercise test–induced ventricular arrhythmias occurred in 146 (10%) of patients evaluated. Compared to those without ETIVA, patients with documented ETIVA had a greater prevalence of abnormal exercise echocardiographic findings and ischemia on exercise echocardiography, greater increase in wall motion score index with exercise, and a greater percentage of abnormal segments with exercise. Similar conclusions were found by McHenry et al[29] in an evaluation of 482 patients with and without CAD. During exercise testing, 27% of patients with angiographic coronary disease experienced ETIVA as compared with only 9% of patients with normal angiograms. Patients with 3-vessel CAD and left ventricular wall motion abnormalities were found to have a significantly greater prevalence of ETIVA. Condini et al[31] described 47 patients with ventricular tachycardia occurring during exercise testing (a prevalence of 0.8% in 5730 treadmill tests). Of the 47 patients, 40 had heart disease, mostly CAD. Ventricular tachycardia was brief and self-terminated in all but one instance. Milanes et al[32] reported a 4.0% prevalence of ventricular tachycardia in 900 treadmill tests performed in patients with CAD compared with less than a tenth percent prevalence in 1700 tests among patients without CAD. Of note, 79% of patients with ventricular fibrillation or tachycardia had an abnormal ST response as well.

Data from other studies have not been in complete accordance. For example, Casella et al[26] evaluated the presence of ETIVA and ischemia in 777 consecutive patients undergoing exercise testing. Although patients with ETIVA were older, with higher blood pressures and peak double products, there was no significant difference found with regard to exercise-induced ischemia.

Our impression from this review and personal experience is that exercise-induced ST depression is not arrhythmogenic whereas exercise-induced ST elevation is very arrhythmogenic and associated with a high risk.

Sex

Bias in many of the previously reported series has also limited their external validity. Few studies have been able to compare ETIVA data from both male and female subjects, and those that do, report disparate findings. The Framingham Heart Study reported that although asymptomatic males with frequent or complex PVCs on

Table 3. Number and Percentage of Subjects with "Ominous" Patterns of PVC Occurrence

Age (y)	n	%
20-29	3	0.8
30-39	7	1.0
40-53	21	3.5

Froelicher et al, AGARD Study, n = 1640 healthy aviators.

ambulatory ECG were at increased risk of mortality, asymptomatic females were not.[33] Jouven et al[21] found ETIVA to be predictive of mortality only when male populations were considered. Whether this represents a true difference in prognosis between males and females is uncertain.

Reproducibility

The issue of reproducibility has further complicated the evaluation of the prognostic significance of ETIVA. Results of studies are not consistently reproducible. Saini et al[34] evaluated the reproducibility of exercise-induced arrhythmias by performing repeat treadmill tests on 28 patients referred for evaluation of ventricular arrhythmia. In half of these subjects, the clinical arrhythmia was sustained ventricular tachycardia or ventricular fibrillation. The prevalence rates of arrhythmia were greater than 80% and did not significantly differ between either test. Excluding infrequent single ventricular premature complexes, the reproducibility of a test with positive outcome was 76%. Thus, it appears that ETIVA are reproducible in patients known to have serious arrhythmias.

In a study performed by Faris et al,[35] 2 serial maximal treadmill exercise tests were performed in a study population of 543 male Indiana State policemen at an average interval of 3 years. Four hundred sixty-two subjects were clinically free of cardiovascular disease and 81 had definite or suspected cardiovascular disease. The prevalence of ETIVA during the first test was 30% in men aged 25 to 34 years, 32% in those aged 35 to 44 years and 36% in those aged 45 to 54 years. The group with definite or suspected cardiovascular disease had a greater prevalence of ETIVA than healthy subjects during both tests, but the prevalence rate with repeat testing remained constant. The occurrence of ETIVA was reproducible in individual subjects during the second test in 55% of 25- to 34-year olds, 58% of 35- to 44-year olds, and 62% of 45- to 54-year olds. Thus, it was concluded that individual reproducibility in 2 consecutive tests was only slightly greater than reproducibility by chance alone. The group with known or suspected cardiovascular disease did demonstrate a trend toward greater reproducibility with repeat testing, although ETIVA were not reproducible by type or complexity. It must be concluded that the marked variability of ETIVA during repeat maximal exercise testing in a clinically normal population appears to negate the usefulness of this finding during a single test as a marker of future cardiovascular disease. However, subjects whose arrhythmias are reproducible may form a group more likely to develop clinical cardiovascular disease in long-term follow-up studies.

Follow-up

Completeness and length of follow-up are both very important features of prognostic studies, as some studies suggest that the risk of ETIVA appear more than 10 years after testing. This makes studying ETIVA more difficult because the longer the follow-up, the greater the risk of losing patients to follow-up. Comorbidities also are important to consider, particularly cigarette smoking and lung disease because they appear to be associated with ETIVA and also affect outcomes. End points that have been used include all-cause mortality, cardiovascular death, sudden death, and MI, as well as surrogate end points including nuclear studies and angiography. The choice of end points greatly affects the results as well as the clinical use of the results. To the clinician wishing to make an intervention that could improve outcome, the prediction of sudden or cardiovascular death or the converse of infarct-free survival is important. Studies using other end points may be less relevant.

Clinical Prognostic Studies

Exercise Test–Induced Supraventricular Arrhythmias

Few studies have evaluated if ETISVA are predictive of an increased risk of cardiac events or death. Atrial arrhythmias may reflect underlying left atrial enlargement and ventricular dysfunction, both prognostic of mortality. A literature search yielded only 2 studies addressing this issue.

Bunch et al[36] performed exercise echocardiography in 5375 patients (aged 61 $\pm$ 12 years) with known or suspected CAD. An abnormal

result was defined as exercise-induced atrial fibrillation (AF)/atrial flutter, supraventricular tachycardia (SVT), or atrial ectopy. A total of 311 patients (5.8%) died (132 [2.5%] from cardiac causes) over a period of 3 years. In addition, 193 patients (3.6%) experienced an MI and 531 patients (9.9%) required revascularization. During exercise testing, 1272 patients (24%) developed atrial ectopy, 185 (3.4%) developed SVT, and 43 (0.8%) developed AF. The 5-year cardiac mortality rate was not statistically different among these groups, but the 5-year incidence of MI was significantly different, highest in the AF group (9%), and with none in the SVT group. The 5-year rate of revascularization among groups was not significantly different (<15%). A composite of all 5-year adverse end points was similar (about 25%). In stepwise multivariate analysis, ETISVA were not predictive of any end point when taking into account traditional clinical variables and exercise test results.

The prevalence, characteristics, and prognostic significance of ETISVA were examined in 843 male and 540 female asymptomatic volunteers aged 20 to 94 years from the Baltimore Longitudinal Study of Aging who underwent exercise testing a mean of 2.3 times between 1977 and 1991.[37] ETISVA occurred during at least 1 test in 51 men (6.0%) and 34 women (6.3%). The 85 subjects with ETISVA were significantly older than the 1298 subjects without ETISVA (66 vs 50 years of age). The prevalence of ETISVA increased with age in men ($P < .001$) but not in women. Most of the 141 discrete episodes of ETISVA were paroxysmal SVT, with heart rates varying from 105 to 290 beats per minute (bpm). Nearly half of ETISVA occurred at peak effort. Coronary risk factors, echocardiographic left atrial size, and the prevalence of exercise-induced ischemic ST-segment depression (11% vs 13%) were similar in 85 subjects with ETISVA and 170 control subjects matched for age and sex. Eight subjects (10%), but only 3 controls (2%), developed AF or paroxysmal SVT 6 years after their index exercise test. Six subjects developed AF; in 4 of these 6 the arrhythmia was sustained. In 2 subjects, paroxysmal AF was observed on ambulatory 24-hour ECG, recorded because of palpitations. The relative risk of developing lone AF during follow-up in subjects with exercise-induced SVT was 8 times. Thus, exercise-induced SVT is not a marker for latent heart disease but is a marker for AF or paroxysmal SVT during the follow-up period.

These 2 studies lead us to the conclusion that ETISVA are relatively rare compared to ventricular arrhythmias and appear to be benign except for a possible relationship to AF.

Exercise Test–Induced Ventricular Arrhythmias

Apparently Healthy Populations

Among patients without any prior evidence of CAD, a majority of studies suggest that ETIVA are associated with increased cardiovascular morbidity or mortality. We describe a representative number of studies and explore the spectrum of results.

A 6-year follow-up study of 1390 male USAF air crewmen referred to the USAFSAM was reported in 1974.[38] The ECG strips were continuously recorded and stored on 8-mm microfilm which was replayed by a trained observer and the arrhythmias recorded retrospectively. Exercise-induced arrhythmias were defined as frequent PVCs at near-maximal or maximal exercise, or 3 consecutive PVCs or more occurring at any time. Frequent PVCs were defined as 10 or more PVCs out of any 50 consecutive beats. Exercise test–induced ventricular arrhythmias were noted in 2.1% of this apparently healthy, select population. Coronary heart disease was defined as onset of angina pectoris, MI, or cardiovascular death. The risk of developing coronary heart disease over the follow-up period among subjects with these arrhythmias was 3 times greater than in those without ETIVA.

In 1989, Busby et al[27] studied 1160 subjects between the ages of 21 to 96 years who underwent treadmill testing an average of 2.4 times. Eighty (6.9%) developed frequent (≥10% of beats in any 1 minute) or repetitive (≥3 beats in a row) PVCs on at least 1 of these tests. Only age appeared to distinguish those with ETIVA, but in these predominantly older, asymptomatic individuals without apparent heart disease, ETIVA did not appear to predict increased cardiac morbidity or mortality.

In 2000, Jouven et al[21] evaluated 6101 asymptomatic Frenchmen between the ages of 42 and 53 years free of clinically detectable cardiovascular disease. Patients underwent exercise testing and were monitored for the presence of 2 or more consecutive PVCs. In their multivariate model, adjustments were made for age, body mass index, resting heart rate, systolic blood pressure, tobacco use, level of physical activity, diabetes, cholesterol, and the presence of PVCs before exercise and during recovery from exercise. The subjects were followed for 23 years for cardiovascular death. They concluded that frequent PVCs (a run of 2 or more making up 10% of any 30 seconds) during exercise in men without detectable cardiovascular disease is associated with a long-term increase in cardiovascular mortality.

An analysis of offspring from the Framingham Heart Study recently reported the results of 1397 men (mean age, 43 years) without known cardiovascular disease who underwent a routine exercise test.[39] Exercise test–induced ventricular arrhythmias were noted in 792 participants (27%) using an off-line Holter type analysis computer system (median, 0.22 PVCs per minute of exercise). Logistic regression was used to evaluate predictors of ETIVA. Cox models were used to examine the relations of infrequent (less than or equal to median) and frequent (greater than median) vs no ETIVA to incidence of "hard" cardiovascular events (MI, cardiovascular death) and all-cause mortality, adjusting for cardiovascular risk factors and exercise variables. Age was a key correlate of ETIVA. During a mean follow-up of 15 years, 113 men had a hard cardiovascular event and 109 men died. Exercise test–induced ventricular arrhythmias were not associated with hard cardiovascular events but were associated with increased all-cause mortality rates (multivariable-adjusted hazards ratio 1.9 for infrequent ETIVA, and 1.7 for frequent ETIVA, vs none). The relationship of ETIVA to mortality risk was not influenced by ETIVA grade, presence of recovery ETIVA, left ventricular dysfunction, or an ischemic ST segment response. In this large, community-based sample of asymptomatic individuals, ETIVA were associated with nearly a doubly increased risk of all-cause mortality at a much lower threshold than previously reported. Surprisingly, the risk is not found isolated to those with cardiovascular end points, making the mechanism less clear.

Referral Patients for Routine Exercise Testing

The next group of studies for selective review includes those based on cohorts of patients referred for exercise testing. The cohorts included a broad spectrum of patients referred to busy clinical labs for the usual clinical indications with the main question being "do they have CAD?"

In 2002, Elhendy and colleagues[30] assessed the occurrence of ETIVA during exercise echocardiography in patients with suspected coronary disease. Their study included 1460 patients (mean age, 64 ± 10 years; 867 men) with intermediate pretest probability of coronary disease. Exercise test–induced ventricular arrhythmias occurred in 146 patients (10%). Compared to patients without ventricular arrhythmias, those with ventricular arrhythmias had a greater prevalence of abnormal exercise echocardiographic findings. During 2.7 years of follow-up, cardiac death and nonfatal MI occurred in 36 patients. After a multivariate analysis of combined clinical and exercise test variables, the authors concluded that independent predictors of cardiac events were ETIVA and maximal heart rate.

Researchers at Cleveland Clinic reported 29 244 patients (56 years of age; 70% men) who had been referred for exercise testing without history of congestive heart failure (CHF), valvular disease, or arrhythmia.[40] Exercise test–induced ventricular arrhythmias were defined by the presence of 7 or more PVCs per minute, ventricular bigeminy or trigeminy, ventricular couplets or triplets, ventricular tachycardia, or ventricular fibrillation. Exercise test–induced ventricular arrhythmias occurred during exercise only in 945 patients (3%), during recovery only in 589 (2%), and during both exercise and recovery in 491 (2%). There were 1862 deaths during a mean of 5.3 years of follow-up. Exercise test–induced ventricular arrhythmias during exercise predicted an increased risk of death (9% vs 5%; hazard ratio [HR], 1.8), but ETIVA during recovery was an even stronger predictor (11% vs 5%; HR, 2.4). After propensity matching for confounding variables, ETIVA during recovery predicted an

increased risk of death (adjusted hazard ratio, 1.5), but ETIVA did not.

At our Veterans Affairs Medical Center in Palo Alto, Calif, Partington et al[41] concluded that the presence of ETIVA is predictive of mortality in a male veteran population. In a retrospective analysis of 6213 consecutive men that were referred for exercise tests, exercise test responses and all-cause mortality were examined after a mean follow-up of 6 ± 4 years. In this study, ETIVA were defined as frequent PVCs constituting more than 10% of all ventricular depolarizations during any 30-second electrocardiogram recording, or a run of 3 or more consecutive PVCs during exercise or recovery. During the analysis, it was discovered that a total of 1256 patients (20%) died during follow-up. Exercise test–induced ventricular arrhythmias occurred in 503 patients (8%); the prevalence of ETIVA was higher in older patients and in those with cardiopulmonary disease, resting PVCs, and ischemia during exercise. Exercise test–induced ventricular arrhythmias were associated with mortality irrespective of the presence of cardiopulmonary disease or exercise-induced ischemia. In those without cardiopulmonary disease, mortality differed more so later in follow-up than earlier. In those without resting PVCs, ETIVA were also predictive of mortality, but in those with resting PVCs, poorer prognosis was not worsened by the presence of ETIVA. We concluded that exercise-induced ischemia does not affect the prognostic value of ETIVA, whereas the arrhythmic substrate does, and furthermore that ETIVA and resting PVCs are both independent predictors of mortality after consideration of other clinical and exercise-test variables. The data were later reanalyzed with cardiovascular mortality as an end point. From this analysis, we learned that ETIVA are independent predictors of cardiovascular mortality after adjusting for other clinical and exercise test variables; their combination with resting PVCs carried the highest risk.[42]

Coronary Artery Disease

In 1984, Sami et al[43] performed a retrospective study to examine the significance of ETIVA in patients with stable CAD from the Coronary Artery Surgery Study. The population included 1486 patients selected from 1975 to 1979, followed for an average of 4.3 years. Patients with coronary disease and ETIVA had similar clinical and angiographic characteristics as compared to those with coronary disease without ETIVA. The only difference discovered was the average ejection fraction (EF), which was 50% for those with ETIVA and 64% for those without ETIVA. The 5-year event-free survival was not influenced by the presence of ETIVA in this study. Using a stepwise Cox regression analysis, the authors concluded that only the number of diseased coronary arteries and the EF were associated with cardiac events. Similar conclusions were drawn by Weiner and Nair in 2 separate studies that same year. Weiner and colleagues investigated ETIVA in a consecutive series of 446 patients who underwent treadmill testing and cardiac catheterization.[28] The prevalence of ETIVA was found to be 19% overall but was 30% in the 120 patients with triple-vessel disease or left main disease. Patients with ETIVA were more likely to have ST depression and abnormal left ventricular function. Despite these findings, at 5 years follow-up, ETIVA were not associated with increased cardiac mortality. In a small study by Nair and colleagues, frequent or complex exercise-induced PVCs were not shown to predict 4-year mortality in patients with coronary disease.[44] Schweikert et al[25] also reported that in patients with documented coronary disease and no prior history of severe ventricular ectopy at rest, exercise-induced frequent or complex PVCs were not predictive of 2-year mortality.

Califf et al[45] studied the prognostic value of ETIVA in 1293 consecutive nonsurgically treated patients in 1983. They defined simple ventricular arrhythmias as at least 1 PVC, but without paired complexes or ventricular tachycardia. In the 236 patients with these simple ventricular arrhythmias there was indeed a higher prevalence of significant coronary disease (57% vs 44%), 3-vessel disease (31% vs 17%), and abnormal left ventricular function (43% vs 24%) than in those patients without any ventricular arrhythmias. Patients with paired complexes or ventricular tachycardia had an even higher prevalence of significant CAD (75%), 3-vessel disease (39%) and abnormal left ventricular function (54%). In the 620 patients with significant CAD, patients

with paired complexes or ventricular tachycardia had a lower 3-year survival rate (75%) than did patients with simple ventricular arrhythmia (83%) and patients with no ventricular arrhythmia (90%).

Even in patients with a documented MI, studies have refuted the proposed relationship between ETIVA and increased risk of cardiovascular death. In 1993, Casella and colleagues[26] reported 777 consecutive patients who underwent a treadmill test at least a year after an MI. The 228 patients who experienced ETIVA were older and had higher blood pressures. No difference was found in the prevalence of exercise-induced ischemia. Furthermore, after 2 years of follow-up, only 5 of the 24 deaths were in patients with ETIVA.

In 1990, Marieb et al[24] analyzed the significance of ETIVA in 383 patients who had undergone both exercise perfusion testing and cardiac catheterization. Two hundred twenty-one patients (58%) had no ETIVA whereas 162 (42%) did. There was no difference between patients with and without ETIVA in terms of previous MI, fixed perfusion defects, number of diseased vessels, and resting EF. In contrast, ischemia (perfusion defect or ST depression) was more likely to be seen in patients with ETIVA. In an 8-year follow-up, patients with ETIVA were shown to be more likely to have cardiac events, although it is unclear if any of these events led to increased mortality.

Patients with Heart Failure

At Cleveland Clinic, an analysis was performed to determine the prognostic importance of ETIVA in recovery among patients with systolic heart failure (HF).[46] Systematic ECG data during rest, exercise, and recovery were gathered on 2123 consecutive patients with left ventricular EF ≤35% who were referred for symptom-limited cardiopulmonary treadmill testing. Severe PVCs were defined as the presence of ventricular triplets, sustained or nonsustained ventricular tachycardia (NSVT), ventricular flutter, polymorphic ventricular tachycardia, or ventricular fibrillation. The primary end point was all-cause mortality, with censoring for interval cardiac transplantation. Of 2123 patients, 140 (7%) had severe ventricular ectopy during recovery and there were 530 deaths over 3 years. Severe ventricular ectopy during recovery was associated with an increased risk of death (3-year death rates, 37% vs 22%; HR, 1.8). After adjustment for PVCs at rest and during exercise, peak oxygen uptake, and other potential confounders, severe PVCs during recovery remained predictive of death (adjusted HR, 1.5), whereas those during exercise was not predictive of death. They concluded that severe PVCs during recovery after exercise is predictive of increased mortality in patients with severe HF and can be used as a prognostic indicator of adverse outcomes in HF cohorts.

Exercise Test–Induced Ventricular Tachycardia

In a retrospective review of 3351 veterans who had undergone routine clinical exercise testing we identified fifty-five patients with exercise test–induced ventricular tachycardia (ETIVT).[47] Nonsustained ventricular tachycardia was defined as 3 or more consecutive ventricular premature beats. Sustained ventricular tachycardia was defined as ventricular tachycardia longer than 30 seconds or requiring intervention. Fifty patients had NSVT during exercise testing and 1 of these patients died because of CHF during the follow-up period. Five patients had sustained ventricular tachycardia during exercise testing and 1 died suddenly 7 months after the test. Ventricular tachycardia was reproduced in only 2 of the 29 patients who underwent repeat exercise testing. Mean follow-up was 2 years. Of the 50 episodes of NSVT, 26 episodes occurred during exercise and 24 occurred in recovery; only 10 occurred at peak exercise and led to cessation of the exercise test. Five patients had exercise-induced sustained ventricular tachycardia; 2 patients had their bouts of ventricular tachycardia during exercise and 3 during recovery. Of these 5 patients, only 2 patients required intervention: 1 was given intravenous lidocaine and 1 was cardioverted because of hypotension. Of the 55 patients with ETIVT, 45 had clinical evidence of CAD; this included 19 with a prior MI, 5 patients who had undergone percutaneous coronary intervention, and 9 patients with prior coronary artery bypass surgery. Two patients had cardiomyopathy and 3

patients had valvular heart disease. Five patients had no clinical evidence of heart disease. The only other episode of a serious ventricular arrhythmia occurring during this period was ventricular fibrillation in a patient without prior cardiac history.

We concluded that nonsustained ETIVT during routine treadmill testing is not associated with complications during testing or with significantly increased cardiovascular mortality within 2 years after testing. In our study, the prevalence and reproducibility of ETIVT were both low (1.2% and 6.9%, respectively), despite a high prevalence of heart disease (mostly CAD) in the study population. The annual mortality among patients with ETIVT was 1.7% compared to 2.4% (171 deaths in 3351 patients) in the study population. Thus, ETIVT during treadmill testing did not portend a worsened prognosis even among our patients with CAD. This statement cannot be extended to the 5 patients with sustained ventricular tachycardia because of their small number and because they were treated.

Complications during exercise testing were reviewed in 25075 consecutive patients, 14037 men and 11038 women, who underwent a total of 47656 maximal treadmill or bicycle exercise tests between April 1985 and March 1999.[48] The mean age of the patients was 53 9 years. Patients undergoing exercise testing to evaluate the efficacy of pharmacotherapy for ventricular tachycardia were excluded. The major reasons for the exercise test were chest pain (27%) and screening (20%). Nonsustained ventricular tachycardia was defined as 8 or more consecutive ventricular ectopic beats at more than 100 bpm. Twenty patients (0.08%) had ETIVT. Of these, 6 patients had ischemic heart disease, 2 had cardiomyopathy, 5 had other cardiac diseases, and 7 patients showed no clinical evidence of heart disease. Ventricular tachycardia occurred at peak heart rates in 12 of the 20 patients.

Detry et al[49] observed 6 cases of ventricular fibrillation and 40 cases of ventricular tachycardia in 7500 consecutive maximal exercise tests (0.6%); 13 patients had sustained ventricular tachycardia and 27 patients had a single short run of ventricular tachycardia. No patient died immediately but 11 patients died during the follow-up. The prognosis was determined by the underlying disease (most often CAD) and the type of arrhythmia. The 5-year survival rate was 84% in patients with a short run of ventricular tachycardia and only 43% in patients with ventricular fibrillation or sustained ventricular tachycardia.

Fleg and Lakatta[22] analyzed data from the Baltimore Longitudinal Study on Aging to evaluate the prognostic impact of ETIVT. Of 597 male and 325 female volunteers between the ages of 21 and 96 years, 10 subjects (7 men and 3 women) with ETIVT (3 consecutive PVCs) were identified, representing 1.1% of those tested; only 1 was younger than 65 years. All episodes were asymptomatic and nonsustained. In 9 of these subjects, the arrhythmia developed at or near peak exercise. The longest run was 6 beats; multiple runs were present in 4 subjects. Two subjects had exercise-induced ST segment depression, but subsequent exercise thallium results were negative in each. Compared with a group of age-matched and sex-matched control subjects, those with asymptomatic, NSVT displayed no difference in exercise duration, maximal heart rate, or the prevalence of coronary risk factors or exercise-induced ischemia as measured by the ECG and thallium perfusion. Over a mean follow-up period of 2 years, no subject developed symptoms of heart disease or experienced syncope or sudden death. Exercise test–induced ventricular tachycardia in apparently healthy subjects occurred mainly in the elderly, was limited to short, asymptomatic runs of 3 to 6 beats usually near peak exercise, and did not predict increased cardiovascular morbidity or mortality rates over a 2-year follow-up.

Exercise Test–Induced Ventricular Arrhythmias in Hypertrophic Cardiomyopathy

In addition to the research examining the prognostic value of ETIVA in patients with coronary disease, studies have also explored the implications of ETIVA in patients with other cardiac disorders such as hypertrophic cardiomyopathy (HCM). It has been proposed that NSVT is only of prognostic importance in patients with HCM when repetitive, prolonged, or associated with symptoms. In 2003, Monserrat and colleagues[50] examined the characteristics of

NSVT episodes during Holter monitoring in patients with HCM in an attempt to determine their relationship to age and prognosis. The study included 531 patients with HCM (323 men, 39 ± 15 years). All underwent ambulatory electrocardiogram monitoring. They found that 104 patients (19.6%) had NSVT and that the proportion of patients with NSVT increased with age (P = .008). Maximum left ventricular wall thickness and left atrial size were greater in patients with NSVT. Mean follow-up for this study was 6 years. Sixty-eight patients died, 32 from sudden cardiac death. Twenty-one patients received an implantable cardioverter defibrillator. There were 4 appropriate defibrillator discharges. In patients 30 years or less, 5-year freedom from sudden death was lower in those with NSVT (78% vs 94%). There was no relationship between the duration, frequency, or rate of NSVT runs and prognosis at any age. The odds ratio of sudden death in patients 30 years or younger with NSVT was 4.4 compared with 2.2 in patients older than 30 years. It appears that NSVT is associated with a substantial increase in sudden death risk in young patients with HCM although a relation between the frequency, duration, and rate of NSVT episodes could not be demonstrated.

Summary

Exercise testing is an important prognostic tool. Poor exercise capacity and exercise-induced cardiac ischemia are known to be strong predictors of mortality, whereas the prognostic significance of exercise-induced arrhythmias is still under debate. Some studies suggest that ETIVA confer a poor prognosis, although others contest this. Less data are available regarding ETISVA. The clinical significance of ETIVA in those without documented cardiovascular disease presents another dilemma. Although studies have found that healthy volunteers with ETIVA had increased mortality, other studies did not produce similar results. It is unclear if the prognosis associated with ETIVA differs based on the presence of cardiovascular disease, ischemic changes during exercise, and/or the presence of PVCs at rest (ie, an indicator of the arrhythmic substrate). We do not advocate cardiac catheterization in all patients with exercise-induced arrhythmias but with otherwise absolutely normal exercise treadmill tests. However, we recognize that this strategy has not been studied and that clinical decisions should be made on an individual basis. In addition, in patients in whom arrhythmias are known to be induced by exercise, exercise testing is an excellent method by which the effectiveness of anti-arrhythmic drug treatment can be assessed, bearing in mind that certain anti-arrhythmic drugs are known to be associated with ETIVT. Table 4 summarizes our review findings.

Needless to say, studies are needed that consider the short comings of previous studies and apply newer Holter-like technologies. The recent Framingham study using such technology to provide PVC counts per minute and finding a risk threshold lower than previously conceived

Table 4. Summary of 22 Clinical Prognostic Studies of Ventricular Ectopy During Exercise Testing

	Results				
			Is Ventricular Ectopy Predictive Of Mortality? (No. of Studies)		
Populations	No. of Studies	Does Ischemia Predict ETIVA? (When Considered)	Rest	Exercise	Recovery
Clinical Population					
Referred for symptoms	8	5 of 6	1	5	1
Known CAD	7	2 of 3	0	2	1
Healthy Population					
Asymptomatic	5	1 of 4	0	1	0
Screening study for employment	2	Not evaluated	0	2	1

The data demonstrate that the majority of clinical studies of exercise testing and arrhythmias have included populations with clinical indications for exercise testing. In these populations, those with symptoms were more likely to have exercise-induced ventricular ectopy that was predictive of mortality. In addition, ischemia was correlated with ETIVA. However, given the limited number of studies and absence of follow-up and assessment of ischemia in some reports, the data remain inconclusive.

should lead to industry efforts to include this capability in commercially available systems. Furthermore, the genomic substrate for arrhythmias should lead to methods of stratifying the risk of individuals with ETIA.

Despite the lack of a consensus in the literature regarding the prognosis of ETIA in a general population, there is sufficient evidence to suggest that clinicians should closely evaluate and follow those patients with arrhythmias during exercise testing. They should aggressively modify risk factors for CAD and cardiomyopathy, and depending upon the nature and severity of the arrhythmia refer for more specific noninvasive testing or for cardiac catheterization.

References

1. Candinas RA, Podrid PJ: Evaluation of cardiac arrhythmias by exercise testing. Herz 15:21-27, 1990
2. Kafka W, Petri H, Rudolph W: Exercise testing in the assessment of ventricular arrhythmias. Herz 7:140-149, 1982
3. Billman GE, Schwartz PJ, Gagnol JP: The cardiac response to submaximal exercise in dogs susceptible to sudden cardiac death. J Appl Physiol 59: 890-897, 1985
4. Friedwald VE, Spence DW: Sudden death associated with exercise: The risk-benefit issue. Am J Cardiol 66:183-188, 1990
5. Verrier RL, Lown B: Behavioral stress and cardiac arrhythmias. Annu Rev Physiol 46:155-176, 1984
6. Gettes LS: Electrolyte abnormalities underlying lethal and ventricular arrhythmias. Circulation 85: 170-176, 1992
7. Schwartz PJ, Billman GE, Stone HL: Autonomic mechanisms in VF due to acute myocardial ischemia during exercise in dogs with healed myocardial infarction: An experimental model for sudden cardiac death. Circulation 69:790-800, 1984
8. Paterson DJ: Antiarrhythmic mechanisms during exercise. Exercise disturbs cardiac sympathovagal and ionic balance. J Appl Physiol 80:1853-1862, 1996
9. Hoffmann A, Wenk M, Follath F: Exercise-induced ventricular tachycardia as a manifestation of flecainide toxicity. Int J Cardiol 11:353-355, 1986
10. Anastasiou-Nana MI, Anderson JL, Stewart JR, et al: Occurrence of exercise-induced and spontaneous wide complex tachycardia during therapy with flecainide for complex ventricular arrhythmias: A probable proarrhythmic effect. Am Heart J 113: 1071-1077, 1987
11. Gosselink AT, Crijns HJ, Wiesfeld AC, et al: Exercise-induced ventricular tachycardia: A rare manifestation of digitalis. Clin Cardiol 16:270-272, 1993
12. Nazari J, Bauman J, Pham T, et al: Exercise induced fatal sinusoidal ventricular tachycardia secondary to moricizine. Pacing Clin Electrophysiol 15:1421-1424, 1992
13. Ranger S, Talajic M, Lemery R, et al: Amplification of flecainide-induced ventricular conduction slowing by exercise. A potentially significant clinical consequence of use-dependent sodium channel blockade. Circulation 79:1000-1006, 1989
14. Tuininga YS, Crijns HJ, Wiesfeld AC, et al: Electrocardiographic patterns relative to initiating mechanisms of exercise-induced ventricular tachycardia. Am Heart J 126:359-367, 1993
15. Kaufman ES, Priori SG, Napolitano C, et al: Electrocardiographic prediction of abnormal genotype in congenital long QT syndrome: Experience in 101 related family members. J Cardiovasc Electrophysiol 12:455-461, 2001
16. Herbert E, Trusz-Gluza M, Moric E, et al: KCNQ1 gene mutations and the respective genotype-phenotype correlations in the long QT syndrome. Med Sci Monit 8:RA240-RA248, 2002
17. Paavonen KJ, Swan H, Piippo K, et al: Response of the QT interval to mental and physical stress in types LQT1 and LQT2 of the long QT syndrome. Heart 86:39-44, 2001
18. Laitinen PJ, Swan H, Piippo K: Genes, exercise and sudden death: Molecular basis of familial catecholaminergic polymorphic ventricular tachycardia. Ann Med 36:81-86, 2004
19. DeBusk RF, Davidson DM, Houston N, et al: Serial ambulatory electrocardiography and treadmill exercise testing after uncomplicated myocardial infarction. Am J Cardiol 45:547-554, 1980
20. Udall JA, Ellestad MH: Predictive implications of ventricular premature contractions associated with treadmill stress testing. Circulation 56:985-989, 1977
21. Jouven X, Zureik M, Desnos M: Long-term outcome in asymptomatic men with exercise-induced premature ventricular depolarizations. N Engl J Med 323:826-833, 2000
22. Fleg JL, Lakatta EG: Prevalence and prognosis of exercise-induced nonsustained ventricular tachycardia in apparently healthy volunteers. Am J Cardiol 54:762-764, 1984
23. Faris JV, McHenry PL, Jordan JW, et al: Prevalence and reproducibility of exercise-induced ventricular arrhythmias during maximal exercise testing in normal men. Am J Cardiol 37:617-622, 1976
24. Marieb MA, Beller GA, Gibson RS, et al: Clinical relevance of exercise-induced ventricular arrhythmias in suspected coronary artery disease. Am J Cardiol 66:172-178, 1990
25. Schweikert RA, Pashkow FJ, Snader CE, et al: Association of exercise-induced ventricular ectopic activity with thallium myocardial perfusion and angiographic coronary artery disease in stable, low-risk populations. Am J Cardiol 83:530-534, 1999
26. Casella G, Pavesi PC, Sangiorgio P, et al: Exercise-induced ventricular arrhythmias in patients with healed myocardial infarction. Int J Cardiol 40:229-235, 1993
27. Busby MJ, Shefrin EA, Fleg JL: Prevalence and long-

term significance of exercise-induced frequent or repetitive ventricular ectopic beats in apparently healthy volunteers. J Am Coll Cardiol 14:1659-1665, 1989

28. Weiner DA, Levine SR, Klein MD, et al: Ventricular arrhythmias during exercise testing: mechanism, response to coronary bypass surgery, and prognostic significance. Am J Cardiol 53:1553-1657, 1984

29. McHenry PL, Morris SN, Kavalier M, et al: Comparative study of exercise-induced ventricular arrhythmias in normal subjects and patients with documented coronary artery disease. Am J Cardiol 37:609-616, 1976

30. Elhendy A, Chandrasekaran K, Gersh BJ, et al: Functional and prognostic significance of exercise-induced ventricular arrhythmias in patients with suspected coronary artery disease. Am J Cardiol 90:95-100, 2002

31. Condini M, Sommerfeldt L, Eybel C, et al: Clinical significance and characteristics of exercise-induced ventricular tachycardia. Catheter Cardiovasc Diagn 7:227-234, 1981

32. Milanes J, Romero M, Hultgren HN, et al: Exercise tests and ventricular tachycardia. West J Med 145: 473-476, 1986

33. Bikkina M, Larson M, Levy D: Prognostic implications of asymptomatic ventricular arrhythmias: The Framingham Heart Study. Ann Intern Med 117: 990-996, 1992

34. Saini V, Graboys TB, Towne V, et al: Reproducibility of exercise-induced ventricular arrhythmia in patients undergoing evaluation for malignant ventricular arrhythmia. Am J Cardiol 63:697-701, 1989

35. Faris JV, McHenry PL, Jordan JW, et al: Prevalence and reproducibility of exercise-induced ventricular arrhythmias during maximal exercise testing in normal men. Am J Cardiol 37:617-622, 1976

36. Bunch TJ, Chandrasekaran K, Gersh BJ, et al: The prognostic significance of exercise-induced atrial arrhythmias. J Am Coll Cardiol 43:1236-1240, 2004

37. Maurer MS, Shefrin EA, Fleg JL: Prevalence and prognostic significance of exercise-induced supraventricular tachycardia in apparently healthy volunteers. Am J Cardiol 75:788-792, 1995

38. Froelicher VF, Thomas M, Pillow C, et al: An epidemiological study of asymptomatic men screened with exercise testing for latent coronary heart disease. Am J Cardiol 34:770-776, 1974

39. Morshedi-Meibodi A, Evans JC, Levy D, et al: Clinical correlates and prognostic significance of exercise-induced ventricular premature beats in the community: The Framingham Heart Study. Circulation 109:2417-2422, 2004

40. Frolkis JP, Pothier CE, Blackstone EH, et al: Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med 348:781-790, 2003

41. Partington S, Myers J, Cho S, et al: Prevalence and prognostic value of exercise-induced ventricular arrhythmias. Am Heart J 145:139-146, 2003

42. Beckerman J, Mathur A, Stahr S, et al. Exercise-induced ventricular arrhythmias and cardiovascular death. Ann Noninvasive Electrocardiol, 2005 (in press)

43. Sami M, Chaitman B, Fisher L, et al: Significance of exercise-induced ventricular arrhythmia in stable coronary artery disease: A coronary artery surgery study project. Am J Cardiol 54:1182-1188, 1984

44. Nair CK, Thomson W, Aronow WS, et al: Prognostic significance of exercise-induced complex ventricular arrhythmias in coronary artery disease with normal and abnormal left ventricular ejection fraction. Am J Cardiol 54:1136-1138, 1984

45. Califf RM, McKinnis RA, McNeer M, et al: Prognostic value of ventricular arrhythmias associated with treadmill exercise testing in patients studied with cardiac catheterization for suspected ischemic heart disease. J Am Coll Cardiol 2:1060-1067, 1983

46. O'Neill JO, Young JB, Pothier CE, et al: Severe frequent ventricular ectopy after exercise as a predictor of death in patients with heart failure. J Am Coll Cardiol 44:820-826, 2004

47. Yang JC, Wesley RC, Froelicher VF: Ventricular tachycardia during routine treadmill testing. Risk and prognosis. Arch Intern Med 151:349-353, 1991

48. Tamakoshi K, Fukuda E, Tajima A, et al: Prevalence and clinical background of exercise-induced ventricular tachycardia during exercise testing. J Cardiol 39:205-212, 2002

49. Detry JM, Abouantoun S, Wyns W: Incidence and prognostic implications of severe ventricular arrhythmias during maximal exercise testing. Cardiology 68:35-43, 1981

50. Monserrat L, Elliott PM, Gimeno JR, et al: Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: An independent marker of sudden death risk in young patients. J Am Coll Cardiol 42:873-879, 2003