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Ambulatory electrocardiographic recordings were obtained from 313 consecutive, totally asymptomatic, male subjects on whom cardiac catheterization was subsequently performed for occupational reasons. These recordings were examined for ventricular ectopy and the results studied in relation to the findings on selective coronary angiography. Ventricular ectopy was a common finding with 58% of those subjects with normal coronary artery anatomy having at least one ventricular premature beat during the period of monitoring (mean 16.5 hours), 22% having greater than one such complex per hour and 10% greater than ten per hour. Complex ventricular ectopy was present in 21% of the normal subjects. No association between the extent or complexity of ventricular ectopy and the presence or grade of anatomical coronary artery disease was demonstrated, nor was ventricular ectopy over represented in those with both significant coronary artery disease on angiography and evidence of ischemia on provocative testing.

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VENTRICULAR ECTOPY IN TOTALLY SYMPTOM-FREE SUBJECTS WITH DEFINED CORONARY ARTERY ANATOMY

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Ventricular ectopy in totally symptom-free subjects with defined coronary artery anatomy

Ambulatory ECG recordings were obtained from 313 consecutive, totally symptom-free male subjects on whom cardiac catheterization was subsequently performed for occupational reasons. These recordings were examined for ventricular ectopy and the results were studied in relation to the findings on selective coronary angiography. Ventricular ectopy was a common finding, with 58% of those subjects with normal coronary artery anatomy having at least one ventricular premature beat during the period of monitoring (mean 16½ hours), 22% having greater than one such complex per hour, and 10% having greater than 10 per hour. Complex ventricular ectopy was present in 21% of the normal subjects. No association between the extent or complexity of ventricular ectopy and the presence or grade of anatomic coronary artery disease was demonstrated, nor was ventricular ectopy overrepresented in those with both significant coronary artery disease on angiography and evidence of ischemia on provocative testing. (Am Heart J 1989;117:1265.)

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The relevance of ventricular premature beats (VPBs) as a predictor of cardiac disease or abnormality has been a contentious subject throughout the history of medicine. Frequent and complex ectopy has been held variously to be associated with an increased probability of ischemic heart disease or sudden death or to be an entirely innocent phenomenon in symptom-free subjects with no clinical evidence of cardiac disease. However, very little information concerning ectopic activity in symptom-free subjects with known coronary artery anatomy has been available, and most surveys have used clinical means and the standard ECG to eliminate coronary artery disease (CAD) in "control" populations. In an attempt to document the range and extent of ventricular ectopic activity in individuals with normal coronary arteries and to define any relationship between such ectopic activity and CAD, we examined the records and ambulatory ECG recordings of 313 symptom-free subjects who underwent cardiac catheterization at the USAF School of Aerospace Medicine (USAFSAM).

METHODS

The records of 348 consecutive subjects, on whom both coronary angiography and computer-analyzed ambulatory ECG recording were performed between June 1984 and September 1987, were reviewed. Of these 348 subjects, 24 had some history of chest pain and were eliminated from further consideration, as were 11 who initially had presented with palpitations. The remaining 313 subjects were essentially symptom-free and were being investigated primarily for reasons associated with flight safety.

The subjects ranged in age from 21 to 66 years (mean 42.4 ± SEM 0.36) and all were men. The majority had been referred for assessment after the finding on routine physical examination, ECG, or other screening test of some abnormality that might be associated with an increased risk of sudden incapacitation in the military aircrew role. In a few cases referral followed previous illness or noncardiac surgery, which required evaluation before clearance for resumption of aircrew duties. Reasons for initial referral are given in Table I. All subjects underwent complete physical examination and full hematologic and biochemical screening.

All individuals were subjected to symptom-limited treadmill exercise testing using the Marquette CASE II signal processor and the USAFSAM-modified Balke protocol.[1] The treadmill exercise ECG was considered abnormal if ST segment depression of 1.0 mm or more at 80 msec after the J point, irrespective of slope, was demonstrated. Exercise thallium scintigraphy and M-mode and two-dimensional echocardiography were performed on all subjects, and ambulatory ECG monitoring for between 11.8 and 26.6 (mean 16.5) hours was performed with a Del Mar twin-channel electrocardiocorder model 449B (Del Mar Avionics, Irvine, Calif.). The tapes were analyzed with a Del Mar Trendsetter II model 9000A electrocardioscanner. Coronary artery fluoroscopy was performed on those subjects over 30 years of age.

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Table I. Reasons for initial referral of subjects to USAFSAM

Initial referral diagnosis	*No.*
Serial ECG changes	
ST-T abnormalities	94
Left ventricular hypertrophy	17
Supraventricular ectopic beats	7
VPBs	27
Right bundle branch block	18
LBBB	9
Left axis deviation	3
Wolfe Parkinson White pattern	4
SVT	7
Miscellaneous	4
Abnormal exercise ECG	24
Cardiac murmurs and possible MVP	35
History of syncope	8
Elevated risk factors for CAD	32
Sarcoidosis	2
Pericarditis	2
Repatriated prisoners of war	3
Migraine	1
Ophthalmic diagnosis	2
ENT diagnosis	1
Post head injury	1
Abnormal pulmonary function	3
Miscellaneous	9
Total	313

MVP, Mitral valve prolapse; ENT, ear, nose, and throat.

Cardiac catheterization was performed either for clinical indications or because full noninvasive investigations suggested that there was a reasonable possibility of coronary artery disease in aviators who wished to retain military flying status. Such occupational indications for cardiac catheterization included abnormal treadmill test results or thallium scintigrams in subjects over 35 years of age or under 35 years of age if associated with significant risk factors for CAD. Other indications were calcification on coronary artery fluoroscopy, acquired left bundle branch block (LBBB), and single episodes of arrhythmia such as supraventricular tachycardia (SVT) or ventricular tachycardia (VT) (Table II). SVT was defined as three or more nonsinus atrial beats in succession at a rate of greater than 100 beats/min and VT as three or more ventricular beats in succession at a rate greater than 100 beats/min.

Cardiac catheterization was performed using the Judkins technique, and the results of coronary angiography were graded according to the most severe lesion demonstrated in a major vessel. Thus the subjects were divided into three groups: those with normal coronary arteries, those with luminal occlusions of <50% of the diameter of the vessel (mild CAD), and those with lesions ≥50% (significant CAD). All these categories were subjected to analysis, because even the milder grades of CAD can be significant in the aeromedical context, particularly when the operational conditions of the military pilot, such as heavy work loads and exposure to high levels of positive G_z, are considered.

Table II. Indications for cardiac catheterization in 313 subjects

Indication	*No.*
Abnormal treadmill exercise ECG	117
Abnormal thallium scintigram	78
Abnormal treadmill and thallium	55
Positive coronary artery fluoroscopy	75
VT	18
SVT	9
Left bundle branch block	6
Aortic insufficiency	5
Follow-up known asymptomatic CAD	3
Rule out myocardial infarction	1

A number of subjects had more than one indication for catheterization.

A subgroup of the group with significant CAD in which the maximal lesion was ≥75% of the luminal diameter (severe CAD) was also considered, and we further evaluated ectopy in that subset of subjects who demonstrated both significant CAD on angiography and reversible ischemia on provocative testing. This latter comparison was made to look specifically for a relationship between ectopy and significant CAD in that subgroup that might be expected to have the greatest likelihood of revealing overrepresentation in ectopy prevalence and complexity: those in whom supply-demand imbalance coexisted with lesions of 50% or greater. Statistical comparisons were performed with the Student unpaired t test and the χ^2 test with Yates' correction for small numbers.

RESULTS

Normal coronary artery anatomy was demonstrated in 202 of our subjects. Sixty-two subjects had mild CAD and 49 were graded as having significant CAD, with 32 of these falling into the severe disease category. VPBs in our symptom-free population of aviators with normal coronary arteries were a common finding. Fifty-eight percent had at least one VPB during the period of monitoring, 22% had more than 1 VPB per hour, 10% had more than 10 per hour, and 7% had more than 50 VPBs per hour (Table III). Twenty-one percent of the normal subjects demonstrated some form of complex ventricular ectopic activity. Among the 202 subjects with normal coronary artery anatomy, multiformity occurred in 12%, VPB pairs in 9%, and bigeminy in 10%. Nonsustained VT was found in five subjects with normal coronary arteries. Removal of the 16 subjects within the normal group who had mitral valve prolapse made no significant difference in these figures.

No association was demonstrated between the extent or complexity of ventricular ectopic activity

Table III. Rates and complexity of VPBs according to coronary artery status

	Normal (%) (n = 202)	*Mild CAD (%) (n = 62)*	*Significant CAD (%) (n = 49)*	*Severe CAD (%) (subgroup n = 32)*
1 or more VPBs	58	62	59	69
VPBs > 1/hr	22	18	22	22
VPBs > 5/hr	15	11	16	13
VPBs > 10/hr	10	10	12	6
VPBs > 50/hr	7	2	10	6
Complex VPBs	21	16	20	19
Multiform	12	13	12	16
Pairs	9	3	10	6
Bigeminy	10	6	8	9
VT	3	3	0	0

No significant differences were detected between normal and diseased groups.

Table IV. Rates and complexity of VPBs in subjects with significant CAD and evidence of reversible ischemia on provocative testing

Coronary artery status	*Total VPBs (1 or more) (%)*	*VPBs > 1/hr (%)*	*VPBs > 5/hr (%)*	*VPBs > 10/hr (%)*	*VPBs > 50/hr (%)*	*Complex VPBs (%)*
Normal (n = 202)	58	22	15	10	7	21
Significant CAD plus						
Abnormal treadmill (n = 28)	61	21	14	4	0	21
Abnormal thallium (n = 26)	58	31	23	15	12	23
Abnormal treadmill and thallium (n = 17)	65	35	23	12	6	24

No significant differences were detected between normal and diseased groups.

Table V. VPBs in subjects with normal coronary arteries related to risk factors and other variables

	None (n = 87)	*1 or more (n = 115)*	*>1/hr (n = 44)*	*>5/hr (n = 30)*	*>10/hr (n = 21)*	*>50/hr (n = 15)*	*Complex (n = 42)*
Age (yr)	40.92	40.87	40.34	39.40	38.48	37.80	40.07
Smoking (cigarettes/day)	6.38	3.13	4.23	3.50	1.67	0	3.10
Caffeine (units/day)	3.11	3.02	3.44	3.37	3.19	3.53	3.29
Alcohol (units/wk)	6.02	6.11	7.40	6.82	6.45	6.57	6.45
Systolic BP (mm Hg)	120.8	121.6	121.7	122.1	121.9	121.7	122.4
Diastolic BP (mm Hg)	78.2	77.0	78.5	78.7	79.8	79.1	77.0
Cholesterol (mg/dl)	209.9	209.0	204.5	205.3	212.1	205.1	200.3
BMI (wt/ht^2)	25.43	25.32	25.24	25.24	25.33	25.44	25.06
Potassium (mEq/L)	4.07	4.08	4.00	3.96	3.92	3.89	4.00

All values are expressed as means; no significant differences were detected.
BP, blood pressure; BMI, body mass index.

and CAD (Table III) or, in those with significant disease, between such ectopy and objective evidence of ischemia on treadmill testing or exercise thallium scintigraphy (Table IV). Multiform and paired VPBs were represented equally in those subjects with normal coronary arteries and those with significant disease. No significant correlation between VPB rates and smoking, alcohol, or caffeine consumption was demonstrable for the group as a whole or for the subgroups with normal and abnormal coronary artery anatomy (Tables V and VI). Nor was there any detectable trend to increased frequency and complexity of VPBs with age within the population that we examined. However, within our

Table VI. VPBs in subjects with significant CAD related to risk factors and other variables

	None (n = 20)	*1 or more (n = 29)*	*>1/hr (n = 11)*	*>5/hr (n = 8)*	*>10/hr (n = 6)*	*>50/hr (n = 5)*	*Complex (n = 10)*
Age (yr)	46.50	45.45	45.09	45.88	44.33	43.20	48.10
Smoking (cigarettes/day)	11.25	12.24	8.64	3.75	5.00	6.00	13.50
Caffeine (units/day)	3.32	4.55	4.36	2.38	2.50	2.00	2.90
Alcohol (units/wk)	6.4	4.62	5.45	4.50	5.17	3.80	7.40
Systolic BP (mm Hg)	124.7	128.2	128.2	131.5	131.7	130.0	133.8
Diastolic BP (mm Hg)	81.9	79.9	78.4	81.9	81.5	79.8	82.4
Cholesterol (mg/dl)	249.5	230.6	229.3	218.0	232.0	237.0	224.9
BMI (wt/ht^2)	26.75	25.50	25.72	25.83	25.65	26.31	25.79
Potassium (mEq/L)	4.12	4.11	3.99	4.05	4.28	4.16	4.03

All values are expressed as means; no significant differences were detected.
BP, blood pressure; BMI, body mass index.

Table VII. Risk factors and other variables according to coronary artery status

Variable	*Normal (n = 202)*	*Mild CAD (n = 62)*	*Significant CAD (n = 49)*	*Severe CAD (subgroup n = 32)*
Age (yr)	40.89 ± 0.44	44.44 ± 0.80*	45.90 ± 0.86*	46.31 ± 1.09*
Cholesterol (mg/dl)	209.4 ± 2.83	219.9 ± 4.84	238.3 ± 7.11*	247.5 ± 9.41*
Cholesterol/HDL ratio	4.84 ± 0.11	5.28 ± 0.21	5.73 ± 0.21†	5.98 ± 0.22*
Potassium (mEq/L)	4.07 ± 0.03	4.19 ± 0.45‡	4.12 ± 0.06	4.11 ± 0.075
Cigarettes/day	4.63 ± 0.72	7.50 ± 1.91	11.84 ± 2.36*	14.22 ± 3.22*
Alcohol (units/wk)	6.10 ± 0.56	5.73 ± 0.77	5.35 ± 1.13	6.28 ± 1.62
Caffeine (units/day)	3.17 ± 0.20	3.02 ± 0.42	4.06 ± 0.57	4.19 ± 0.80
BMI (wt/ht^2)	25.36 ± 0.17	25.91 ± 0.30	26.02 ± 0.31	25.48 ± 0.34
Exercise (hr/wk)	1.54 ± 0.13	1.64 ± 0.20	0.84 ± 0.18‡	0.66 ± 0.22‡

Numbers are expressed as mean ± SEM.
HDL, High-density lipoprotein; BMI, body mass index.
Significant differences when compared with the normal group:
*$p < 0.001$; †$p < 0.01$. ‡$p < 0.05$.

study group there was a strong association between the presence of significant CAD and the commonly accepted risk factors of age, smoking, and serum cholesterol levels (Table VII).

DISCUSSION

It is well established that ventricular ectopic activity tends to increase with age,[2-5] but whether this has any pathologic significance as a marker for CAD, or as a harbinger of sudden death, is less certain and has been the subject of considerable controversy over the years. Some large studies have suggested that the finding of VPBs on routine 12-lead ECGs is associated with an increased risk of developing symptomatic ischemic heart disease and sudden death.[3,6,7]

Other surveys that have used ambulatory ECG monitoring have suggested that VPBs are more common in subjects with significant CAD[5,8] and that there may be a correlation between the frequency and complexity of such ectopic activity and the extent of disease and the level of risk of sudden death.[8,9] However, such studies have been challenged by other groups of workers who have failed to confirm any such relationship[4,10] and by surveys that have demonstrated frequent and complex ectopy on ambulatory ECG monitoring in such diverse groups as apparently healthy teenage boys,[11] medical students,[12] working men and women of various ages,[13-16] and clinically healthy elderly people.[17] Equally, the follow-up of a cohort of subjects with frequent and complex ectopy in the absence of CAD (as demonstrated by angiography) has revealed a good prognosis for the group during a 10-year period.[18] However, what is more widely accepted is that ventricular ectopic activity is more common after myocardial infarction[2] and that in that situation it may have some predictive value for mortality that is independent of other risk variables.[19,20]

A major hurdle to the further understanding of

Table VIII. Studies of ventricular ectopy in healthy subjects

Reference	*Authors*	*Year*	*Subjects*	*No.*	*Age (yr)*	*Disease excluded by*	*Findings*
11	Dickinson and Scott	1984	Teenage boys	100	14-16	History and examination	VPBs in 41%: multiform in 30%, VT in 3 subjects
12	Brodsky et al.	1977	Male medical students	50	23-27	History, examination, ECG, chest x-ray, echocardiography	VPBs in 50%: multiform in 12%, VT in 1 subject
15	Sobotka et al.	1981	Young women	50	22-28	History, examination, ECG, chest x-ray, echocardiography	VPBs in 54%: 6% > 50 in 24 hr, VT in 1 subject
14	Romhilt et al.	1984	Working women	101	20-60	History, examination, ECG, chest x-ray	VPBs in 34%: complex in 10%
16	Orth-Gomer et al.	1986	Working men	147	15-65	History, examination, ECG, lipids	Age < 40 yr: 95% have <3 VPBs/hr; age > 39 yr: 95% have <36 VPBs/hr; VPBs increase with age
13	Clarke et al.	1976	Working men and women	86	16-65	History, examination, ECG, lab data	VPBs in 73%: multiform in 15%, > 5/hr in 8%, VT in 2 subjects
17	Fleg and Kennedy	1982	Active elderly men and women	98	60-85	History, examination, ECG, treadmill, thallium	VPBs in all but 2 subjects: 17% > 100 VPBs in 24 hr; 12% > 30 VPBs/hr; 5 runs VT in 4 subjects
22	Kostis et al.	1981	Men and women (99 with chest pain, 2 with high lipid levels)	101	16-68	Full noninvasive tests, cardiac catheterization	VPBs in 39%: 5% > 5/hr; VPBs increase with age

the significance of ventricular ectopic activity in symptom-free subjects has been the relative paucity of studies in which the cardiac rhythm has been examined in relation to known coronary artery anatomy in this group. Most studies of ventricular ectopy in symptom-free "healthy" subjects have excluded CAD by clinical means, routine resting ECG, and occasionally more extensive noninvasive investigations (Table VIII). However, noninvasive tests are known to have poor predictive value for CAD in symptom-free subjects,[21] and very few surveys have included angiographic data. Of those studies in subjects who were shown to have normal coronary arteries on catheterization, the largest involved a population who were being investigated for unexplained chest pain or suspected CAD and who were far from being symptom free.[22] Other surveys have been directed primarily at investigating patients who had florid ventricular ectopy in the absence of other evidence of cardiac disease.[23, 24]

The subjects in our study were symptom-free aviators who were subjected to regular scrutiny of their health status for occupational reasons primarily concerned with flight safety. They were a highly selected group but, as in most population surveys, ventricular ectopy was a common finding among these individuals, and indeed 27 of them (9%) had been referred specifically for assessment of this phenomenon. The total lack of any correlation between this ventricular ectopic activity and the anatomic coronary artery status of the subjects, including those in whom provocative test results for myocardial ischemia were positive, lends support to the view that, unless specifically associated with a known cardiac abnormality, VPBs can be regarded as a benign incidental finding in the symptom-free individual. Furthermore this finding appears to be true regardless of the rate or complexity of these ectopic beats or the risk factor status of the subjects in the population that we studied. We are left with the conclusion that ventricular ectopy has no useful contribution to make in the prediction of the types of anatomic CAD that can be discovered in totally symptom-free middle-aged men by noninvasive testing. Furthermore such ventricular ectopy affords no means of risk stratification in the search for asymptomatic coronary lesions of occupational importance. However, the possibility of a weak

association between ventricular ectopy and CAD still cannot be entirely discounted, because of the limited power of a study of this population size (n = 313) to detect very small differences between the normal and the diseased groups.

From a prevalence standpoint this study demonstrates how difficult it is to infer a causal relationship specifically between ventricular ectopy and CAD, because VPBs were not overrepresented in those with the most severe coronary artery lesions or in those with objective evidence of myocardial ischemia during noninvasive testing. Thus the pursuit of ventricular ectopy as a marker of asymptomatic CAD would appear to have no justification on a population basis. These observations have important implications for occupational medical screening programs, including the assessment of cardiac status in aircrew. The finding of frequent ectopy would not appear to predict asymptomatic CAD, but in the younger individuals clinical and echocardiographic examination to exclude structural abnormalities would be appropriate, together with a routine biochemical screen. In the older subject (>35 years) the decision whether to pursue tests that might predict asymptomatic CAD should probably be based on clinical assessment and risk factor analysis rather than on the presence or extent of ventricular ectopy alone. Finally, it must be acknowledged that in those patients with known significant CAD, complex ectopy cannot necessarily be dismissed as unrelated, because causality can neither be proved nor disproved in the individual case.

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