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Cardiac Functioning and Blood Pressure of 47,XYY and 47,XXY Men in a Double-Blind, Double-Matched Population Survey

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SUMMARY

This paper reports the electrocardiogram measures and blood pressure of 12 men with 47,XYY, 14 men with 47,XXY, and 52 matched controls with 46,XY. The abnormal karyotypes were identified in a systematic population search for XYY and XXY men. The subjects and their matched controls were examined in a double-blind fashion.

Electrocardiogram measures of 47,XYY and 47,XXY men were found to differ from those of 46,XY controls. The XYYs had longer P-R intervals, shorter QRS complexes, and nonsignificantly longer R-R intervals than their matched controls. The XXYs showed longer R-R intervals and trends for prolonged P-R intervals and shorter QRS complexes when compared with their controls. Trends toward increased within-group variability in the XYY and XXY groups were observed in five of six variance tests, suggesting that the sex chromosome aneuploids have a cardiac conduction anomaly.

Blood pressure measures of 47,XYY and 47,XXY men were found not to differ from those of 46,XY men. None of the measures revealed a significant difference between the XYYs and the XXYs.

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INTRODUCTION

As part of an extensive investigation of the relationship between sex chromosome aneuploidy and physical, psychological, and social factors, we examined the cardiac functioning of XYY and XXY men who had been identified in an unbiased population survey [1, 2]. This paper describes our analyses for systolic and diastolic blood pressure, the P-Q(R) interval, the length of the QRS complex, and the R-R interval in the electrocardiogram (EKG).

Price [3] first called attention to cardiac functioning in XYY men. Subsequent reports on a total of 92 XYYs identified in various ways suggested a prolonged mean P-Q(R) interval of .177 second [4–8]. This compared with 88 control XYs' mean P-Q(R) interval of only .156 second [3, 8]. Some data are also available on 74 XXYs, suggesting a mean P-Q(R) of .166 second [3, 8]. One search for XYYs has even been conducted by examining EKGs for P-R intervals greater than .20 second [9], a length which occurs in the general population with a frequency less than 0.65% [10, 11].

No significant differences have been demonstrated for the QRS complex among any of these previously studied groups. The difficulty in determining the end point of the QRS complex coupled with the shortness of the interval may have contributed to this failure. The R-R intervals of the 47,XYY and 47,XXY men were .925 and .945 second, respectively. The R-R for the 46,XY men was .875 second [8].

Several individual case reports on XYYs indicate normal blood pressure [3, 5, 12–14]. Richards and Stewart [15] described an XYY with relatively low blood pressure, and Marinello et al. [16] reported one XYY case with high blood pressure; however, in this latter case, a sister also had high blood pressure. Blood pressure in XXYs has been reported as within normal limits in those case reports where mentioned, but a systematic study of blood pressure in XXYs cannot be found in the literature. Hellström [17] reported an average blood pressure of 131.4/75.6 mm Hg for normal men with a mean age of 20. Lygonis [18] found mean blood pressure to be 131/81 mm Hg in a group of men ranging from 26 to 30 years.

MATERIALS AND METHODS

Subjects

The starting population for this study consisted of all 31,436 men born from January 1, 1944, through December 31, 1947, whose mothers were officially registered as inhabitants of Copenhagen when they gave birth. The heights of all these men, surviving to adulthood, were collected, and chromosome analyses were completed in 4,139 of the men who reached adult heights of 184 cm or more. In this way, 12 XYYs and 16 XXYs were identified. Further details of this case-finding procedure are provided by Witkin et al. [1] and Philip et al. [2].

All 12 of the XYYs and 14 of the XXYs agreed, without being informed of their chromosomal status, to participate in an individual case study. During this phase of the study, each proband was matched with two control XYs (also selected from among the 4,139 men who had been karyotyped), and all of these men underwent an intensive two-day examination in a double-blind design. Each member of one control group, C-1, was matched to his proband for age, adult height, and parental social class on the day the subject was born. The other group, C-2, was matched for performance on an intelligence-screening test in addition to being matched for age, adult height, and parental social class. Thus, the 78 men in the

double-blind individual case study included the 12 XYYs and their 24 matched controls plus 14 XXYs and their 28 matched controls. All participants were from age 26 to 31 at the time of the EKG and blood pressure examination.

Cardiac Measures

Blood pressure was measured from the upper right arm, following 5 min of relaxation with a flat pillow, using a mercury manometer, 12 cm manchet, and ERCA balloon.

For the EKG, subjects were placed in a semireclining position, each in the same chair, at the same place, and during the same time of day. A Beckman R Dynograph made a paper recording (30 mm/second) of the EKG and, simultaneously, of the electroencephalogram. An FM analog magnetic tape recording was created in addition to the paper record. In two cases, which were later shown to be an XXY and an XXY's C-2 subject, the magnetic tapedeck was not functioning during recording of the EKG; thus, the R-R intervals of these two men are missing.

The subjects received a stimulus sequence while the EKG was recorded. The sequence consisted of ten 80 dB 1 kHz tones, lasting 1 second each, with intertrial intervals ranging from 30 to 50 seconds. These served as orienting trials for the purpose of stimulus habituation in another part of the sex chromosome project.

The P-R interval was defined as the interval from the beginning of the upstroke of the P wave to the beginning of Q or R. Measurements of the P-R interval were taken from the paper record, with the aid of a transparent template, by E. B. before he was informed of the subject's group membership. Four different P-R measurements were averaged to obtain each subject's P-R score.

The QRS complex was defined as the distance from the beginning of Q or R to the point where the S wave, or the extrapolation of the upstroke of S, crossed the isoelectric line. Four QRS measurements were taken from the paper record and averaged to provide each subject's QRS score. While it was rather easy to get a constant value for the P-R interval on each subject, the QRS complex was less well defined. Consequently, there is a rather large intraindividual variance in the QRS measurements. In one case, later shown to be an XXY, the QRS could not be defined clearly because of a bundle-branch block configuration with changing QRS; the QRS complex ranged from .13 to .17 second in that case.

Computer analysis of the magnetic tape records provided the R-R interval. The analog tape was processed by electronic circuits to produce artifact-free pulses coinciding with the RS-downslope of the QRS waves. (Sandman et al. [19] provide details of the circuit.) These pulses were input to a PDP-11/40 program that determined R-R intervals with a resolution of 1 millisecond. Each subject's score is the average of 250 heartbeats—the 10 beats before and the 15 beats after each of the 10 stimuli in the habituation sequence.

Drug Influence on the EKG

Cardiac function, and consequently different parts of the EKG, may be influenced by a variety of drugs. Therefore, in conjunction with the EKG recording procedure, a urine sample was taken from each subject and analyzed by thin-layer chromatography for the presence of nitrazepam, chlordiazepoxide, diazepam, morphine, codeine, methadone, and amphetamine. The urine of two subjects contained aspirin; another subject's urine contained aprobarbital. Otherwise, the urine was apparently free of these drugs.

In addition to the urine samples, the physician interviewed each subject about the use of drugs that might influence the EKG. These interviews produced no evidence of drug use that would influence the recorded EKGs.

RESULTS

The mean scores for every measure are shown in table 1 for each of the six groups. The cardiac measures were each subjected to an analysis of variance in which the

TABLE 1

MEAN CARDIAC SCORES FOR EACH GROUP

	XYY No. = 12	C-1 No. = 12	C-2 No. = 12	XXY No. = 14	C-1 No. = 14	C-2 No. = 14
P-R interval (seconds)	.179	.155	.165	.171	.152	.159
R-R interval (seconds)	.949	.845	.877	.942*	.857	.845*
QRS complex (seconds)	.097	.108	.105	.100	.110	.106
Systolic blood pressure (mm Hg)	130.4	138.3	132.9	128.6	135.4	131.1
Diastolic blood pressure (mm Hg)	78.33	81.25	76.25	78.93	82.50	78.57

*No. = 13 for R-R because of equipment malfunction. Missing scores were conservatively replaced by the mean R-R from the 76 subjects with complete data prior to the analysis of variance in table 3.

XYYs and their two control groups were contained in one matched set, and the XXYs and their two control groups constituted a second matched set. Thus, three matched groups were nested in a set—the respective proband, C-1, and C-2 groups. Because matched-groups designs of this sort are positively biased by violations of the assumptions placed on the variance-covariance matrix, conservative tests have been performed following the $\tilde{\epsilon}$ procedure described by Huynh [20]. The adjusted degrees of freedom for the conservative tests are reported in parentheses in the analysis summary tables, and all reported significance levels reflect the conservative tests.

P-R Interval

Table 2 summarizes the analysis of variance on the P-R interval. Although the groups main effect was nearly significant ($P < .06$), interest should focus instead on

TABLE 2

ANALYSIS OF VARIANCE ON P-R CARDIAC INTERVAL

Source	df (adjusted df)	Mean square	F	P
Groups in set*	4	$.1525 \times 10^{-2}$	2.53	.0526
Simple XYY groups	2	$.1769 \times 10^{-2}$	2.93	.0627
Contrast 1†	1	$.2939 \times 10^{-2}$	4.87	.0161‡
Contrast 2§	1	$.6000 \times 10^{-3}$	1.00	.3235
Simple XXY groups	2	$.1280 \times 10^{-2}$	2.12	.1308
Contrast 1†	1	$.2270 \times 10^{-2}$	3.77	.0582
Contrast 2§	1	$.2893 \times 10^{-3}$	0.48	.4918
Replications × groups in set	48	$.6029 \times 10^{-3}$	...	...
Sets	1	$.7239 \times 10^{-3}$	1.17	.2905
Replications in set	24	$.6197 \times 10^{-3}$	...	...
XYY vs. XXY contrast	1	$.4660 \times 10^{-3}$	0.77	.3844
Pooled error term	(72)‖	$.6085 \times 10^{-3}$	...	...

*Huynh $\tilde{\epsilon} = 1.0$.
†Contrast 1 compares proband group to combined control groups in one set.
‡One-tailed test.
§Contrast 2 compares C-1 to C-2 in one set.
‖Satterthwaite [21] approximation for pooled replications in set plus replications × groups in set error term.

a further partitioning of that source of variance since the previous reports lead to the specific hypothesis that XYYs have a longer P-R interval than XYs. The groups main effect can be partitioned into two independent simple effects (one for each set), which can each be further partitioned into two independent contrasts. Within either set, contrast 1 compares the proband group mean with the average of its C-1 and C-2 means; contrast 2 tests the equality of the C-1 and C-2 means within a set. Among the XYYs and their controls, contrast 1 was significant ($P < .02$; a one-tailed test is appropriate as the direction of the effect was predicted a priori). The XYYs had a significantly longer P-R interval than their XY controls. Two of the XYYs (17%) had P-R intervals greater than .20 second, being .24 and .21 second, respectively. The XYY control groups, however, did not differ ($P > .32$).

No a priori hypothesis for the XXYs has been given about the P-R interval. But contrast 1 for the XXY groups indicated a trend ($P < .06$) in which the XXYs also had a longer sample P-R interval than their XY controls. Three of the XXYs (21%) had P-R intervals greater than .20 second, being .22 second in each. As expected, the XXY control groups did not differ ($P > .49$).

A contrast can also be constructed that compares the XYYs with the XXYs. In these data, however, there was no evidence of any XYY-XXY mean difference on the P-R interval ($P > .38$).

R-R Interval

The R-R analysis of variance is summarized in table 3. The literature review tentatively suggested that the R-R intervals for the XYYs and XXYs may be prolonged, so one-sided tests are appropriate. Among the XYY set, contrast 1 showed a trend ($P < .07$), and table 1 confirms that the sample mean R-R interval was longer in the XYYs than in their matched XY controls. No difference appeared between the two control groups (contrast 2: $P > .62$).

TABLE 3

ANALYSIS OF VARIANCE ON R-R CARDIAC INTERVAL

Source	df (adjusted df)	Mean square	*F*	*P*
Groups in set*	4	37326.32	1.46	.2321
Simple XYY groups	2	34040.58	1.33	.2756
Contrast 1†	1	61776.13	2.41	.0639‡
Contrast 2§	1	6305.04	0.25	.6225
Simple XXY groups	2	40612.06	1.58	.2168
Contrast 1†	1	80645.70	3.14	.0416‡
Contrast 2§	1	578.43	0.02	.8813
Replications × groups in set	48(44)	25650.11	...	...
Sets	1	946.79	0.05	.8296
Replications in set	24	19989.72	...	...
XYY vs. XXY contrast	1	83.84	0.00	.9528
Pooled error term	(66)‖	23763.31	...	...

*Huynh $\tilde{\epsilon} = .910$.

†Contrast 1 compares proband group to combined control groups in one set.

‡One-tailed test.

§Contrast 2 compares C-1 to C-2 in one set.

‖Satterthwaite [21] approximation for pooled replications in set plus replications × groups in set error term.

For the XXY set, contrast 1 showed a significant difference ($P < .05$), and table 1 again confirms that the R-R interval was longer in the XXYs than in their matched XY controls. As expected, the two XXY control groups did not differ (contrast 2: $P > .88$). The contrast directly comparing the XYYs and XXYs on the mean R-R interval was nonsignificant in these data ($P > .95$).

QRS Complex

The analysis of variance summary for the QRS complex is contained in table 4. The literature review provided no directional hypotheses about the QRS complex for either proband group. But the planned contrasts pinpoint a significant difference between the XYYs and their matched controls (contrast 1: $P < .04$). Table 1 shows that the XYYs had a shorter QRS complex than their XY controls.

Within the XXY set, contrast 1 showed a trend ($P < .08$), and table 1 indicates that the XXYs also had a shorter sample mean QRS complex than their XY controls. Contrast 2 showed no significant difference between the two XY control groups for either set ($P > .41$ in each). The contrast directly comparing the two proband groups showed no significant XYY-XXY effect on mean QRS for these data ($P > .58$).

Blood Pressure

No significant differences emerged in the analysis of variance for systolic blood pressure. In particular, there was no significant mean difference between the XYYs and their controls ($P > .13$), and there was no significant mean difference between the XXYs and their controls ($P > .14$). No significant difference between C-1 and C-2 appeared in either set ($P > .17$ in each). The XYY and XXY means did not differ in systolic blood pressure either ($P > .62$).

TABLE 4

ANALYSIS OF VARIANCE ON CARDIAC QRS COMPLEX

Source	df (adjusted df)	Mean square	F	P
Groups in set*	4	$.3476 \times 10^{-3}$	2.27	.0763
Simple XYY groups	2	$.3901 \times 10^{-3}$	2.25	.0893
Contrast 1†	1	$.7136 \times 10^{-3}$	4.67	.0362
Contrast 2‡	1	$.6667 \times 10^{-4}$	0.44	.5124
Simple XXY groups	2	$.3050 \times 10^{-3}$	2.00	.1480
Contrast 1†	1	$.5085 \times 10^{-3}$	3.33	.0749
Contrast 2‡	1	$.1016 \times 10^{-3}$	0.66	.4193
Replications × groups in set	48 (44)	$.1528 \times 10^{-3}$	...	...
Sets	1	$.5215 \times 10^{-4}$	0.19	.6694
Replications in set	24	$.2791 \times 10^{-3}$	...	...
XYY vs. XXY contrast	1	$.5866 \times 10^{-4}$	0.30	.5849
Pooled error term	(64)§	$.1949 \times 10^{-3}$	...	...

*Huynh $\tilde{\epsilon} = .926$.

†Contrast 1 compares proband group to combined control groups in one set.

‡Contrast 2 compares C-1 to C-2 in one set.

§Satterthwaite [21] approximation for pooled replications in set plus replications × groups in set error term.

The diastolic blood pressure analysis of variance revealed no significant mean differences between the probands and their controls in either set ($P > .57$ in each), and there were no significant differences between the C-1 and C-2 groups in either set ($P > .16$ in each). The XYYs did not differ in mean diastolic blood pressure from the XXYs in these data ($P > .86$).

Within-group Variability on Cardiac Measures

Increased variability on cardiac measures has been reported by Price et al. [8], who suggested that the sex chromosome aneuploidy is associated with a cardiac conduction anomaly leading to greater dispersion about the mean value. For each set in our study, a one-tailed F ratio can be constructed to test the hypothesis that the within-group variance for the proband group is greater than the pooled within-group variance for the appropriate C-1 plus C-2 groups. For both XYY and XXY sets, and in every one of the EKG measures, the sample variance is larger in the proband group than it is in either of the respective control groups. Of the six within-group variance tests, two were significant ($P < .04$), three more showed trends ($P < .10$), and one was considered nonsignificant ($P > .13$).

DISCUSSION

Cardiac functioning, as revealed by these EKG measures, in XYY and XXY men appears to differ from that of XY men, although the XYY and XXY groups seem similar to one another. Comparing the XYYs and their XY controls, this study confirmed earlier reports of a prolonged P-R interval and also found a shortened QRS complex in the XYYs. The XYYs' mean R-R interval was also longer, but not significantly so in these data. There were no mean differences in blood pressure for the XYYs.

None of the XYYs showed any clinical evidence of cardiac abnormality, such as atrial septal defect, which could account for the prolonged P-R interval. Age above 50 years could not be implicated in this XYY group either. Pharmacological factors had also been minimized on the basis of an interview coupled with urine studies by thin-layer chromatography.

The general picture was quite similar for the XXYs, who showed a significantly lengthened R-R interval, and trends toward a prolonged P-R interval and shortened QRS complex when compared with their XY controls. No differences emerged for blood pressure, however.

Clinical and electrocardiographic evidence of cardiac abnormality was present in one XXY, who had a family history of cardiac disease. This man exhibited extrasystoles clinically, and the average QRS complex was .14 second in his EKG. These findings suggest a highly unusual ventricular conduction defect for a man of his age [22].

There were no significant mean differences between the XYYs and XXYs on any of these cardiac measures, nor were there any significant differences on within-group variability between the XYYs and XXYs on any of these measures.

The mean P-R intervals in this study correspond very well with earlier reports. The XYY mean P-R of .179 agrees almost perfectly with the report of .180 by Price

et al. [8]. For the XXYs, our mean P-R of .171 is very close to the Price [3] value of .169. Our average P-R for all 52 XYs in this study was .158, which compares quite favorably with the .157 for XYs reported by Price et al. [8] and the .16 reported by Simonson [10].

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