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Effect of β-adrenergic blockade on beat-to-beat response to Valsalva manoeuvre[1]

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Ten normal male volunteers received either 100 mg alprenolol or placebo in a double-blind randomized trial. Ninety minutes later they performed a standardized Valsalva manoeuvre 40: mmHg airway pressure for 12 seconds. Beat-to-beat measurements were made of heart rate, left ventricular ejection time (LVET), ejection time index (ETI), and 'corrected ejection time' ($LVET/\sqrt{cycle}$).

After placebo, heart rate, left ventricular ejection time, and ejection time index followed essentially the same beat-to-beat patterns as the normal response reported previously. β-blockade produced qualitatively similar curves, but with increased cycle length and reduced left ventricular ejection time per beat at all points. Both ejection time index and corrected ejection time curves did not differ significantly between placebo and alprenolol for corresponding phases. β-blockade, therefore, reduced control and subsequent heart rate so the Valsalva strain was sustained and completed with fewer heart beats during the standard time but with a pure rate effect on ejection time. This effect on the time-course of the Valsalva heart rate indicates that the same reflex response occurs but at a lower parallel set during β-blockade.

The Valsalva manoeuvre has long provided a safe, standardizable, noninvasive test which has proved useful in investigating both physiological and pathological cardiocirculatory responses (Gorlin, Knowles, and Storey, 1957; Levin, 1966; Sarnoff, Hardenbergh, and Whittenberger, 1948; Greenfield *et al.*, 1967; Fox *et al.*, 1966; Flessas, Kumar, and Spodick, 1970). The Valsalva manoeuvre divides naturally into a pair of sequential challenge states: *strain* and *release*. Previous investigations demonstrated the applicability of noninvasive polygraphic methods to the Valsalva manoeuvre, and that beat-to-beat analysis yields lower coefficients of variation than does time-based analysis (Flessas *et al.*, 1970; Chirife and Spodick, 1972). Measurements of systolic time intervals showed that the preejection period did not change significantly but heart rate and ejection time showed very characteristic phasic beat-to-beat patterns of response during the strain and post-release periods. These phases were characterized by directional trends each of which occur within a narrow range of beats after strain and release.

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Sarnoff and colleagues (1948) demonstrated the usefulness of the Valsalva manoeuvre as an indicator of the integrity of the sympathetic nervous system, particularly in connexion with baroreceptor reflex heart rate control in normal individuals. More recently, Leon, Shaver, and Leonard (1970) challenged this result because in their study β-adrenergic blockade in 4 subjects apparently failed to elicit significantly different rate responses during a Valsalva strain. They concluded that Valsalva-induced heart rate changes were not suitable for testing sympathetic function.

We evaluated the effect on beat-to-beat analysis of the Valsalva manoeuvre of aplrenolol, an agent producing β-adrenergic receptor blockade comparable to that of propranolol (Kerber *et al.*, 1972; Trinker and Carson, 1971; Spodick, Meyer, and St. Pierre, 1972). A double-blind randomized trial using placebo control was designed. The results were plotted beat by beat and compared on the basis of the beat-to-beat phases of the Valsalva manoeuvre previously demonstrated (Flessas *et al.*, 1970).

Subjects and methods

Ten normal, active male volunteers, ages 22 to 35, re-

ceived either 100 mg alprenol or placebo identical in appearance on different days on a double-blind random trial. Ninety minutes later they performed a previously practised standardized Valsalva manoeuvre, sustaining 40 mmHg airway pressure ('strain') for 12 seconds (Flessas *et al.*, 1970). Subjects were continuously monitored before and during strain and after release from strain with electrocardiographic lead II and right carotid pulse using Hewlett-Packard no. 2100D pulse-wave pick-up. Beat-to-beat heart rate was measured as 60,000/RR interval in milliseconds. Left ventricular ejection time (LVET) (Spodick and Kumar, 1968) was measured from the rapid upstroke to the incisura of the carotid pulse. Rate-correction of LVET was done by two methods: calculation of ejection time index (ETI) using the reported regression relation for normal subjects (Spodick, Dorr, and Calabrese, 1969): ETI = LVET + 1·2 HR, and by 'LVETc', i.e. LVET divided by the square root of cycle length: $LVETc = LVET/\sqrt{R\text{-}R}$.

Blind procedure

Measurements and calculations were made without knowledge of whether the subject had received placebo or alprenolol. When all the data had been recorded for each subject and all measurements and calculations were completed, the code was broken. The numerical results of 'placebo runs' and 'drug runs' were then plotted together and submitted to statistical analyses.

Breakdown of results and statistical analyses

Beat-to-beat trend charts (Flessas *et al.*, 1970) were plotted for heart rate and for left ventricular ejection time. Each common point of inflection (delineating phases) was established for each subject. The mean beat number and mean value (± SD and SE, respectively) of heart rate or left ventricular ejection time were calculated for all subjects for both placebo and alprenolol. These data were each compared by the paired t-test for differences. Additionally, a three-dimensional analysis of variance (Lindquist, 1953) was performed on left ventricular ejection time and heart rate, testing for effects caused by treatment and by observation sequence and their interaction. In cases where the analysis of variance was statistically significant the data were then tested for critical differences.

Validation of β-adrenergic blockade

On two different days each, four consecutive subjects received at random either 100 mg alprenolol or placebo in identical, coded capsules. Ninety minutes later isoprenaline 0·03 μg/kg per min was infused for 5 minutes. Heart rate response was monitored and recorded. The code was broken after all 8 isoprenaline challenges had been measured. In every case cardioacceleration by isoprenaline occurred after placebo (mean HR change: +14·50 beats/min) and was blocked by alprenolol (mean HR change: +2·75 beats/min.)

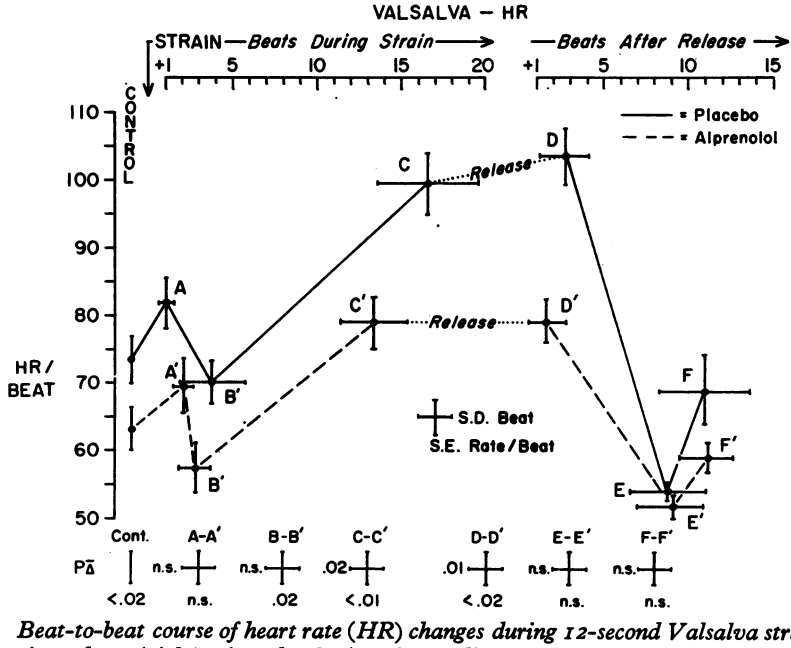

FIG. 1 *Beat-to-beat course of heart rate (HR) changes during 12-second Valsalva strain (left) and following release (right) after placebo (continuous line), and β-blockade by alprenolol (interrupted line). Mean values for control, end-strain (C and C'), and points of inflection demarcating phases plotted for beat number (horizontal scale) and heart rate (vertical scale), with respective SD and SE. At bottom: point-by-point statistical result for rate (vertical bars) and beat number (horizontal bars).*

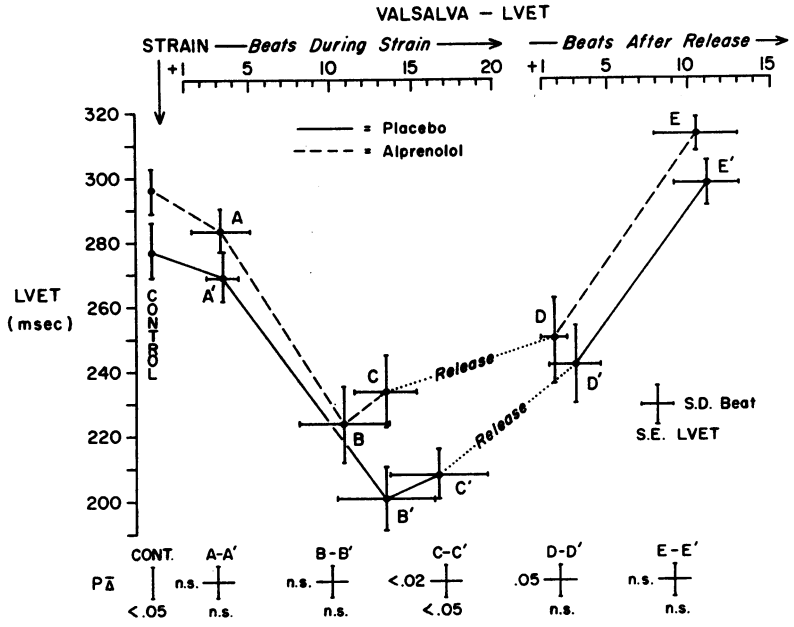

FIG. 2 *Beat-to-beat course of ejection time (LVET) changes during 12-second Valsalva strain (left) and following release (right) after placebo (continuous line) and β-blockade by alprenolol (interrupted line). Mean values for control, end-strain (C and C'), and points of inflection demarcating phases plotted for beat number (horizontal scale) and LVET (vertical scale) with respective SD and SE. At bottom: point-by-point statistical result for LVET (vertical bars) and beat number (horizontal bars).*

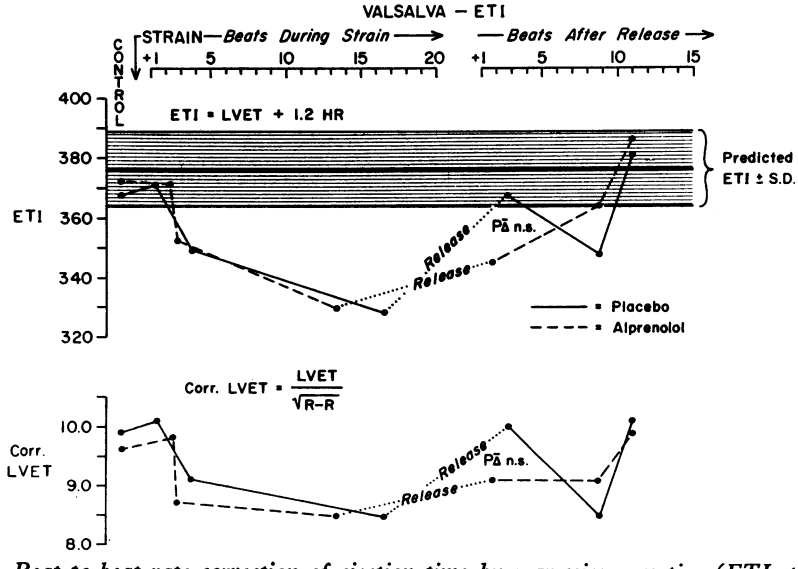

FIG. 3 *Beat-to-beat rate correction of ejection time by regression equation (ETI, top) and 'LVETc' (bottom). Shaded zone of values for ejection time index corresponds to predicted ETI at theoretical zero heart rate established in comparable subjects. By both methods, curve changes correspond to those expected for Valsalva strain and release, but alprenolol (interrupted line) produces no significant changes (P̄Δn.s.) from placebo (continuous line)*

Results

Results are summarized in Fig. 1, 2, and 3. For both placebo and alprenolol, both heart rate and left ventricular ejection time responded in essentially the same phasic beat-to-beat patterns as previously reported; these are depicted in Fig. 1 and 2 (Flessas *et al.*, 1970).

Heart rate response (Fig. 1)

Alprenolol progressively slowed heart rate. Significant differences from placebo occurred at control (difference = −10·3 beat/min), early strain bradycardia ('lowest'; −12·8 beats/min), end-strain tachycardia ('end-strain'; −20·56 beats/min) and at post-strain 'initial rise' (−24·7 beats/min). Significant differences disappeared during the later post-release bradycardia and rebound.

Beat number Because of the heart rate slowing, 'end-strain' (standardized at 12 seconds) was reached at a mean of 3·2 beats earlier ($P = 0.02$) because of alprenolol. With the release phase (beginning the second physiological challenge state), the post-release 'initial rise' occurred 1·1 beat earlier ($P = 0.01$) because of alprenolol.

Response of left ventricular ejection time (Fig. 2)

Both control and 'end-strain' left ventricular ejection time were longer ($P < 0.05$ each) after alprenolol.

Beat number 'End-strain' was reached earlier (mean −3·2 beats; $P < 0.02$) as was the post-release 'initial rise' (−1·2 beat; $P = 0.05$).

Ejection time index and 'corrected ejection time' (Fig. 3)

Correcting for heart rate effect on LVET by both ETI and 'LVETc' ($LVET/\sqrt{R\text{–}R}$) in each case resulted in elimination of significant differences at all points.

Discussion

After both placebo and β-adrenergic blockade, heart rate, left ventricular ejection time, and ejection time index each followed essentially the same qualitative beat-to-beat time course as previously reported (Flessas *et al.*, 1970). β-blockade resulted in increased cycle length per beat and increased left ventricular ejection time per beat at control and toward end-strain and the early post-release period. However, at no point did ejection time index and 'LVETc' differ significantly between placebo and alprenolol. β-blockade, therefore, significantly reduced control and subsequent heart rates so that the Valsalva strain was sustained with fewer heart beats (i.e. lower beat number at the end of the standard 12 sec time), but with any effects on ejection time dependent solely on rate differences.

The very significant rate effect of β-adrenergic receptor blockade with alprenolol contrasts with the findings of Leon and colleagues (Leon *et al.*, 1970) who studied 4 subjects and found no significant difference in the rate response during Valsalva strain after β-blockade with propranolol despite a decrease in control heart rate similar to the alprenolol effect in our subjects. We cannot account for these quantitatively divergent results excepting for possible differences in β-blocking agents (which seems to be an unlikely explanation) (Kerber *et al.*, 1972; Trinker and Carson, 1971) and differences in their study, i.e. smaller number of subjects, intravenous administration of propranolol, inclusion with other challenges, and absence of statistical evaluation in this part of their report. There is little doubt of the objectivity of our results both because of the quantitatively large effect of alprenolol (NB – Fig. 1, B-B′, C-C′, and D-D′), and because bias was minimized by a double-blind randomized design. On the other hand, the quantitative changes from control to strain to release in both studies are directionally the same, so the conclusions from this effect need not differ.

Left ventricular ejection time varies inversely with heart rate and directly with stroke volume (SV). As demonstrated by the beat-to-beat ejection time index, the Valsalva manoeuvre imposes a pronounced divergence from the expected rate relation (shaded area in Fig. 3). This implies stroke volume changes caused by decreased filling. That this does in fact correspond to stroke volume changes is indicated by the striking agreement of our results on a beat-to-beat basis with the stroke volume changes during the Valsalva strain and release reported by Greenfield and colleagues (1967), and close resemblance to the curve of changes in aortic flow reported by Fox and colleagues (1966). The values for both ejection time index and 'LVETc' showed no differences between placebo and alprenolol at corresponding points, implying that β-adrenergic receptor blockade had a pure rate slowing effect.

Valsalva rate-responses are particularly important as a reliable index of cardiac performance (Gorlin *et al.*, 1957; Levin, 1966; Sarnoff *et al.*, 1948). The effect of β-block with alprenolol on the Valsalva rate-response indicated that β-sympathetic activity does not alter its pattern, but does have a significant role in setting its level (Gorlin *et al.*, 1957; Levin,

1966; Sarnoff *et al.*, 1948; Flessas *et al.*, 1970; Franklin, Van Citters, and Rushmer, 1962). During β-blockade as opposed to the control state a comparable reflex heart rate response occurs at a lower parallel set.

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