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Indices of Cardiac Function During Treatment with Betamimetic Drugs (Fenoterol and Hexoprenaline)

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Summary. The limiting factor in the treatment of preterm labor by betamimetics is the effect of these drugs on heart rate and cardiac action.

In this paper we compare these effects produced by hexoprenaline and fenoterol, which are both β-sympathomimetic drugs now in clinical use. As indices of cardiac action we measured the pre-ejection period (PEP), the left ventricular ejection time (LVET) and their sum, namely total electromechanical systole (QS_2) by thoracic impedance cardiography.

In 20 individual tests, seven subjects were given both hexoprenaline and fenoterol on separate occasions in a dose relationship of 1 : 12.5.

We found a relation between PEP/LVET on the one hand and the Heather-index (an impedance specific parameter of response to stress) on the other. Both parameters represent inotropic effects in cardiac action.

With increasing betamimetic stimulation there was a decrease of PEP/LVET (−23% for hexoprenaline and −29% for fenoterol) and an increase in the Heather-index (+98% for hexoprenaline and +117% for fenoterol). These results are not statistically significantly different and so we cannot agree with Lipshitz [19] who reported less β1-stimulation with hexoprenaline.

Key words: Betamimetics – Thoracic impedance cardiogram – Systolic time intervals – Hexoprenaline – Fenoterol

Introduction

Betamimetic drugs are commonly used for the treatment and prevention of preterm labor. Besides the desired tocolytic effect, the betamimetics induce β2-mediated alterations in hemodynamics, namely vasodilatation, a reduction of

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peripheral vascular resistance and a consequent fall in diastolic blood pressure.

Despite a high $\beta 2$-selectivity of the newer tocolytic drugs, dose-dependent concomitant reactions occur in the maternal cardiovascular system, which seem to be variously pronounced in different individuals. These reactions can also be interpreted as the result of a $\beta 1$-stimulation and are manifested as an increase in heart rate and ventricular function. Whereas alterations in heart rate are easily measured by continuous monitoring, changes in ventricular function can only be measured accurately by elaborate methods. A recognized technique is the determination of various systolic time intervals, namely the pre-ejection period (PEP), the left ventricular ejection period (LVET) and their sum (total electromechanical systole or QS_2) [5, 13, 16, 18, 21, 29–31]. These time intervals can be measured from simultaneous recordings of the ECG, the carotid pulse wave and the phonocardiogram.

Thoracic impedance cardiography, primarily employed by Kubicek and Karnegis [14] for noninvasive measurement of cardiac output, also gives information about systolic time intervals [4, 11, 27], which correlates well with measurements based on invasive or echocardiographic techniques [4, 11, 25, 32].

According to Heather [8] the so-called Heather-index (HI) is calculated as the quotient of:

dz/dt (first derivate of Delta-Z, the gross impedance change during the cardiac cycle) and

R–Z interval (interval between maximum electrical stimulation of the myocardium [R-wave of ECG] to the point of peak ventricular ejection [Z, highest spike of the dz/dt-curve] (see Fig. 1).

This quotient, derived from thoracic impedance cardiogram may serve as an indicator of the ability of the myocardium to respond to stress.

Our objective was to study indices of cardiac action during the administration of the betamimetic drugs hexoprenaline and fenoterol. According to Lipshitz et al. [19], Lipshitz and Baillie [20], and Reinold [26] hexoprenaline (a di-aminoethanol synthesized by molecule doubling) is a good tocolytic agent with few reported cardiovascular effects [12, 28, 33]. The literature contains no information about alterations of systolic time intervals, which is of interest since Lipshitz et al. [19] reported hexoprenaline to have more pronounced $\beta 2$-selectivity.

In addition the present study includes an analysis of the relation between the systolic time intervals and (a) the Heather-index as well as (b) the peak value of dz/dt, which is directly proportional to the peak aortic flow rate [15].

We also calculated the relation between PEP and the R–Z time interval.

Methods and Subjects

Our investigations were performed with the IFM/Impedance cardiograph, model 304 (marketing in West-Germany: Diefenbach GmbH, Frankfurt). Two autoadhesive aluminium electrode bands were put around the neck 3 cm apart and two further electrodes were placed 3 cm apart at the lower thoracic inlet. A constant, sinusoidal alternating current of 4 mA, 100 kHz was passed longitudinally

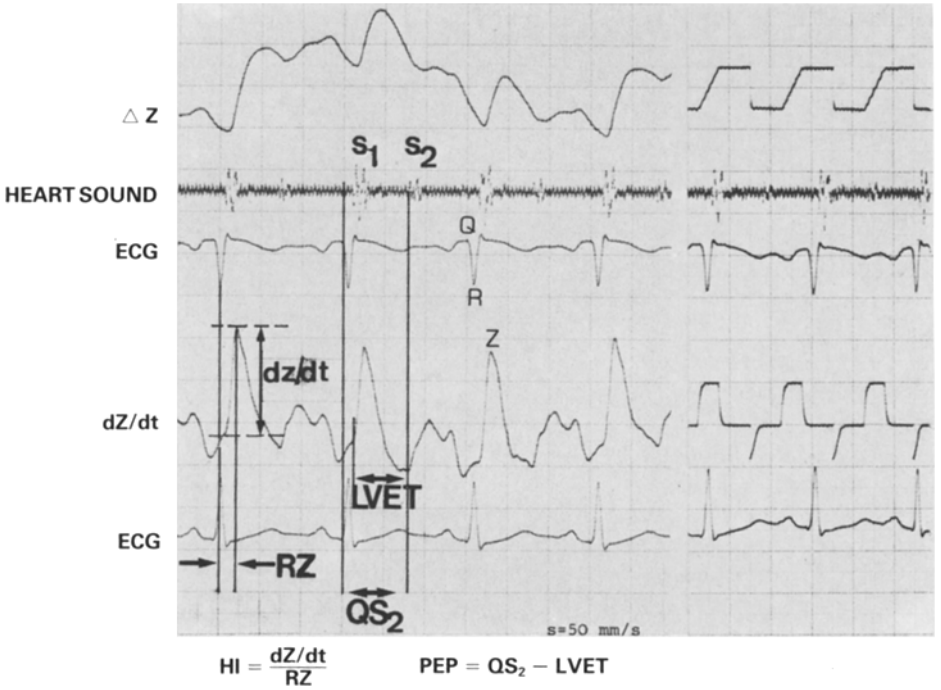

Fig. 1. Thoracic impedance cardiogram showing: (1) systolic time intervals, (2) Heather-index

through the thorax between the two outer electrodes, the two inner electrodes being used to record digitally the changes in thoracic impedance during the cardiac cycle. An external ECG (leads II and aVL) was recorded and a crystal microphone was applied just lateral to the sternum to record the heart sounds. ECG, phonocardiogram, the impedance signal ΔZ and the first derivate of ΔZ (dz/dt) were recorded synchronously via a multichannel plotter (Mingograf, Siemens). We followed the recommendations of Erbel and Belz [7] and calculated systolic time intervals from the arithmetic mean of five consecutive cardiac cycles during a resting mid-respiratory phase. We used a built-in ZCG-computer (Diefenbach GmbH, Frankfurt), triggered by two potentiometers, which indicated the respective distance of the internal electrode bands and the specific hematocrit-dependent resistance of the blood [15]. This computer calculated the Heather-index from one cardiac cycle to another from the analogue signals of the impedance cardiograph. The values were recorded automatically by a built-in thermoprinter. The pulse rates were derived from the ECG-recordings.

All investigations were performed in the afternoon to eliminate diurnal fluctuations [16, 18] in systolic time intervals. We studied 13 healthy young student volunteers (seven male, six female) (see Table 1). In seven of the subjects investigated both hexoprenaline and fenoterol were given in separate experiments, the interval between experiments ranging from 48 h (in one volunteer) to 6 months (four volunteers), so that a total of 20 experiments were performed. In subjects given both drugs, the first was chosen by random allocation. There were no statistically significant differences between the two groups with regard to age, height, weight and sex.

All subjects were asked to consume no coffee, tea or alcohol during the day preceding the investigation. After putting on the electrode bands and adopting the supine position, subjects were kept resting until reproducible measurements could be obtained. Hexoprenaline (H) was given by i.v. infusion for 1 h at a dose of 0.2 μg/min and fenoterol (F) was given at a dose of 2.5 μg/min. For the crossover group, we calculated a body weight-related dose of 0.0033 μg H/kg b.wt./min and 0.0412 μg F/kg b.wt./min, giving a dose relationship of 1 : 12.5.

All measurements were made at 15 min intervals, using cardiac cycles in the mid-respiratory phase.

Table 1. Characteristics of patients in study

	Fenoterol (2.5 µg/min)	Hexoprenaline (0.2 µg/min)
Total number/sex (♂, ♀)	9 4, 5	11 6, 5
Cross over	7	
Age (years)	24.2 ± 2.0	25.2 ± 4.7
Cross over	24.2 ± 2.2	
Body weight (kg)	59.6 ± 7.4	63.7 ± 9.2
Cross over	60.0 ± 7.9	
Body height (cm)	170.7 ± 9.4	173.5 ± 9.7
Cross over	170.7 ± 10.3	

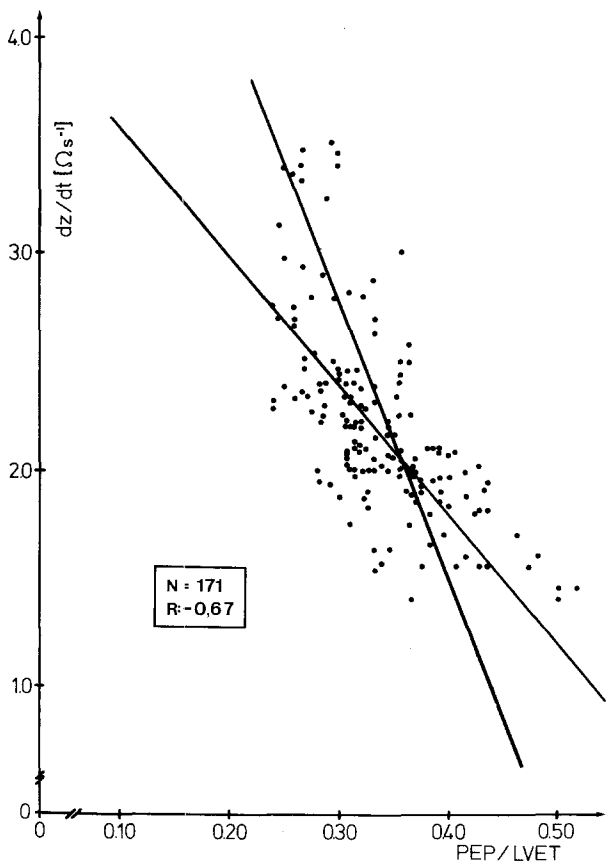

Fig. 2. Correlation between PEP/LVET and dz/dt

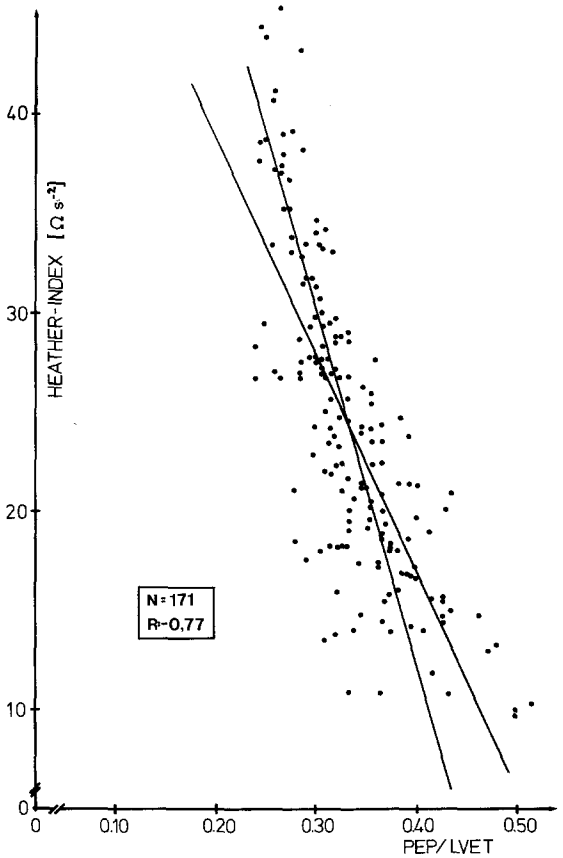

Fig. 3. Correlation between PEP/LVET and Heather-index

Statistics

At the Biometric Centre of Therapy Studies, Society for Information Processing and Statistics in Medicine, Munich, analysis of variance (5% level) were performed for the type of drug and duration of treatment.

Results

Figure 1 shows an actual recording with the indices of ventricular function mentioned below. The electromechanical systole QS_2 extends from the beginning of the Q-wave to the beginning of the second heart sound (S_2), which coincides with the end of the dip in the thoracic impedance signal dz/dt signalling the end of the ejection phase. With technically inadequate dz/dt-signals, a phonocardiogram recording is indispensable for precise timing of the end of QS_2 or LVET. The LVET-interval lasts from the beginning of the initial steep rise of dz/dt to the beginning of the second heart sound. PEP is obtained by subtracting LVET from QS_2. The parameters used to calculate the Heather-index are the R−Z interval (in s) and the dz/dt amplitude (in Ω/s).

Table 2. Changes in QS_2, PEP/LVET, Heather-index, heart rate and stroke volume during administration of hexoprenaline and fenoterol

Time (min)	Parameter									
	QS_2 (s)		PEP/LVET		HI (Ω/s^2)		HR (beats/min)		SV (ml)	
	Drug									
	H	F	H	F	H	F	H	F	H	F
0	0.565 ± 0.021	0.561 ± 0.013	0.366 ± 0.023	0.399 ± 0.048	16.74 ± 2.23	15.43 ± 3.96	66 ± 10	66 ± 6	85.4 ± 30.4	83.5 ± 18.9
15	0.553 ± 0.022	0.538 ± 0.023	0.313 ± 0.021	0.337 ± 0.046	24.72 ± 2.47	28.29 ± 7.92	71 ± 10	86 ± 8	107.8 ± 36.4	112.5 ± 32.9
30	0.544 ± 0.016	0.542 ± 0.024	0.302 ± 0.024	0.311 ± 0.041	28.80 ± 3.82	31.59 ± 8.54	75 ± 11	91 ± 10	111.1 ± 39.0	109.6 ± 33.2
45	0.546 ± 0.018	0.528 ± 0.021	0.291 ± 0.025	0.289 ± 0.031	31.70 ± 6.84	33.04 ± 5.74	81 ± 11	95 ± 7	111.5 ± 38.9	108.1 ± 27.5
60	0.538 ± 0.017	0.523 ± 0.020	0.282 ± 0.027	0.289 ± 0.034	33.18 ± 6.28	33.47 ± 5.89	85 ± 11	96 ± 7	107.0 ± 36.4	108.2 ± 31.6

H = Hexoprenaline; F = Fenoterol

Correlation Analysis

The correlations were based on 171 single measurements. The systolic time intervals, obtained when the pulse rate was more than 110 beats/min as a result of betamimetic stimulation were excluded from the following correlation analysis.

Figure 2 shows the linear correlation between PEP/LVET and dz/dt as stroke volume equivalent [15]. Calculating

$$y = 4.02 - 5.36\ x \text{ and } x = 0.52 - 0.08\ y$$

the correlation coeffizient is $r = -0.67$.

The linear correlation between PEP/LVET and HI (Fig. 3) gives a coeffizient of $r = -0.77$ with

$$y = 0.47 - 0.01\ x \text{ and } x = 61.51 - 110.88\ y.$$

There is a linear correlation of $r = 0.77$ between PEP as calculated value from QS_2-LVET and the R–Z interval from the impedance cardiogram.

On the basis of these correlations, the Heather-index was adopted as an index of cardiac action in addition to the systolic time quotient PEP/LVET.

Indices of Cardiac Action During Treatment with Hexoprenaline and Fenoterol

Since a dose-activity comparison related to body weight is needed for a comparative pharmacological study, the results we now present relate to the cross-over group where the dose ratio between hexoprenaline and fenoterol was 1 : 12.5.

Table 2 summarizes the QS_2, PEP/LVET, HI and heart rate results with the hematocrit-corrected calculations for stroke volume [14]. With increasing betamimetic stimulation there was a marked decrease in total electromechanical systole, accompanied by a fall in PEP/LVET while the Heather-index, as would be expected, showed a significant increase.

At rest the values for PEP/LVET were in the normal range specified by Weissler [31]. The diastolic blood pressure at rest was nearly identical in both groups (H: 73 ± 9 mm Hg, F: 74 ± 9 mm Hg) and we found a similar fall during treatment with H (60 ± 13 mm Hg) as with F (62 ± 9 mm Hg) at 60 min administration of the drugs. These changes in diastolic blood pressure were presumably due to $\beta 2$-mediated peripheral vasodilatation.

Figure 4 shows the PEP/LVET and HI throughout the 60 min period and also gives percentage changes compared to the baseline values.

Statistics

The changes of PEP/LVET and HI were not significantly different when fenoterol and hexoprenaline were compared ($p = 0.05$).

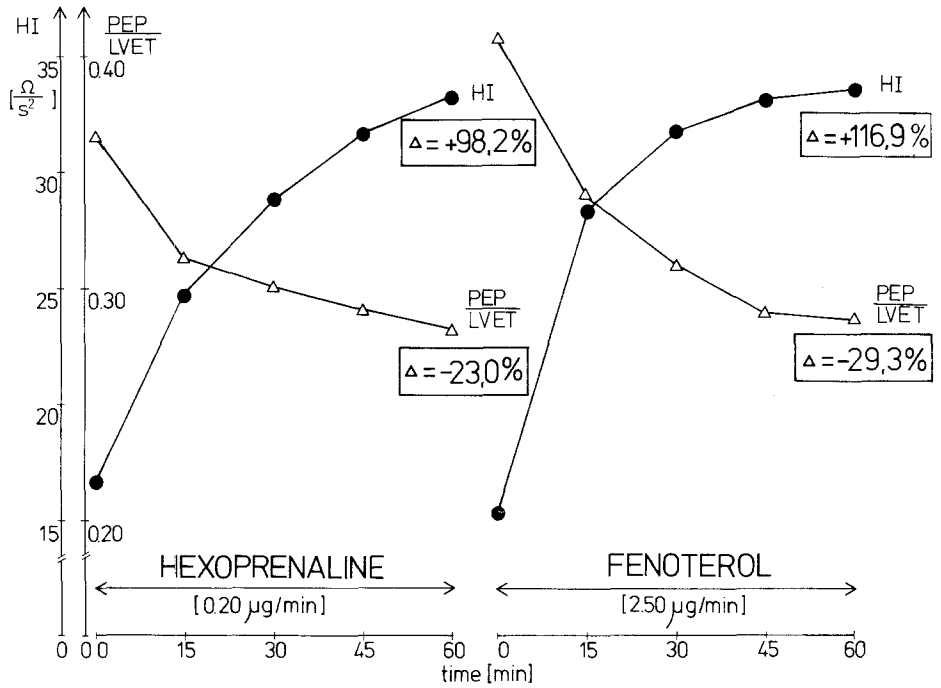

Fig. 4. Changes of PEP/LVET and Heather-index with time

Discussion

Lands et al. [17] inaugurated the differentiation between $\beta 1$- and $\beta 2$-receptors while Carlsson et al. [6] pointed out that there is no absolute organ-specific distribution of $\beta 1$- and $\beta 2$-receptors. This theory has been confirmed experimentally by Minneman et al. [23] and Hedberg et al. [9] and is the reason why we chose to study different aspects of concomitant cardiac reactions due to "$\beta 2$-selective" tocolytic agents such as fenoterol or hexoprenaline.

The increase in heart rate cannot be regarded as the sole parameter for $\beta 1$-stimulation during treatment with "$\beta 2$-tocolytics", since heart rate is also influenced by means of the baroreceptor reflex [24]. In contrast, a part of the increase in heart rate may be due to the direct effect of $\beta 2$-mimetics on the $\beta 2$-receptors of the sinus node [1]. Thus the measurement of contractility-associated parameters is necessary for precise evaluation of the effect of tocolytic drugs on cardiac action. According to the experiments of Hedberg et al. [9] the vast majority of beta receptors in the left ventricle are of the $\beta 1$-type.

The literature about the effects of hexoprenaline on the maternal cardiovascular system reports varying results [12, 19, 20, 26, 28, 33] and they chiefly relate to alterations of heart rate and blood pressure. In a previous study [28], using invasive (Swan-Ganz catheter) and non-invasive (impedance cardiography) techniques simultaneously, we found a 20% rise in stroke volume with both hexoprenaline and fenoterol, when their dose ratio was 1 : 12.5.

Hiltmann [12] reported a maximum rise of 65% in the Heather-index with hexoprenaline (0.30 μg/min). With 0.05 μg fenoterol/kg b.wt./min, the Heather-index rose by more than 100% above the initial value. In a prospective randomised study with two groups of 50 patients, who alternatively received fenoterol or hexoprenaline in a dose ratio of 1 : 8, Heilmann and Siekmann [10] described an increase in cardiac output of about 25% with hexoprenaline and nearly 30% with fenoterol/verapamil. In an alternating clinical study using fenoterol and hexoprenaline (dose ratio: 1 : 12.5) Arabin et al. [3] was able to show that both betamimetics had comparable tocolytic activity.

An important characteristic of β1-adrenergic stimulation of the heart is the change in ventricular action, which can be quantified by alterations in the systolic time intervals. According to Weissler et al. [31], β-receptor stimulation of the heart by isoproterenol leads to a significant decrease of the PEP/LVET time quotient. We agree with Johnson et al. [13], that the heart rate-dependent lowering of QS_2 is a practical, readily reproducible measure of response of the ventricle to drugs, which have not major influence on the end-diastolic ventricular filling pressure or the systemic blood pressure. Others have found very good correlations analysis between systolic time intervals on the one hand and left ventricular contractility and pressures measured by invasive methods [2, 13, 22]. Various authors [5, 16, 21, 29] point out the significance of sex, age, diurnal fluctuations and body posture in the clinical assessment of systolic time intervals. According to Weissler et al. [30], sex-specific regression equations are commonly used to take into account the heart rate. These equations relate the systolic time intervals to the hypothetical heart rate value 0. Using the PEP/LVET time quotient [30], this correction needs not to be applied when the heart rate is between 50–110 beats/min.

Non-invasive impedance cardiography enables the determination of both the systolic time intervals and the Heather-index. Our calculations reveal a correlation coefficient of $r = -0.77$ between the Heather-index and PEP/LVET during treatment with betamimetic drugs. Our results are in good agreement with those of Hill and Merrifield [11], who compared the two parameters in healthy subjects in various postures. With regard to the β1-mediated effects on ventricular function, analysis of the PEP/LVET ratio and the Heather-index revealed no statistically significant differences between the two betamimetics hexoprenaline and fenoterol in a body weight-related dose ratio of 1 : 12.5. Unlike Lipshitz et al. [19], we did not find that hexoprenaline had a higher β2-selectivity than fenoterol in doses, which had comparable tocolytic activities.

We propose to study the effect of using a β1-selective inhibitor, metoprolol, in combination with hexoprenaline.

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