Systolic time intervals in measurement of inotropic response to drugs

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SUMMARY During periods of tachycardia induced by atrial pacing in eight patients, moderate increments in dP/dt(max) and (dP/dt)/CPIP (common produced intraventricular pressure) and moderate reductions in left ventricular ejection time (LVET) and Q–S_2 were demonstrated. These changes varied between individuals, but reduction in systolic intervals was consistently less than that reported from populations showing a range of resting heart rates. Individual regression formulae relating each variable to paced heart rate were used to calculate rate-dependent and rate-independent changes induced by isoprenaline and ouabain. Despite technical difficulty in precise measurement of systolic intervals, there was an excellent inverse correlation between rate-independent changes in Q–S_2 and in both dP/dt(max) and (dP/dt)/CPIP. Rate-independent change in Q–S_2 appears to be a practical, moderately sensitive, and reasonably precise measure of the inotropic effect of a drug which does not radically alter left ventricular end-diastolic pressure or blood pressure. Day-to-day variation in systolic intervals may limit the use of the technique to studies of short duration.

Determination of the inotropic activity of a drug essentially belongs to the animal laboratory, but confirmation of this activity, and particularly characterisation of its dose-response effects in man, is a necessary prelude to its rational clinical employment. Direct measurement of changes in contractile activity and pumping function of the left ventricle presently furnish the most accurate indication of alterations in inotropic activity.[1-3] Cardiac catheterisation, however, is cumbersome, limited by ethical considerations, and often of such brevity as to preclude the measurement of duration of activity of a drug or its dose-response effects. Non-invasive methods have therefore been sought as a means of making repeated measurements of left ventricular activity; among such methods measurement of the duration of the various components of systole has been the most widely acclaimed.[4-6] The utility of these methods, however, in evaluating changes in left ventricular activity induced by drugs has yet to be fully tested. It was the purpose of this study, therefore, to evaluate the precision by which measurements of non-invasive systolic time intervals

reflect changes in intraventricular pressure before and after the administration of drugs known to increase inotropic activity.

Subjects and methods

Four normal subjects (aged 20 to 35 years), and six male and two female patients (aged 23 to 45 years) admitted for the investigation of chest pain were studied. All were in sinus rhythm. In the patients, radiographic cardiac silhouette was normal. Electrocardiograms at rest and during treadmill exercise up to heart rates of 160 beats per minute were normal in all. Left ventricular end-diastolic pressure during supine leg exercise did not exceed 25 mmHg. None was receiving drugs at the time of the study. Informed consent was obtained from all patients.[7 8]

DESIGN OF INVESTIGATION
The four normal subjects were used to determine the day-to-day variation in systolic time intervals. Measurements were made on separate days at the same time each morning two hours after a light breakfast without tea or coffee and after they had been quietly reclining for 20 minutes.

Patients were studied resting supine without sedation two hours after a light meal. Left ventricular

catheterisation was performed by the percutaneous Seldinger technique via the right brachial artery using a (55×0·1 cm) red Portex nylon catheter with a frequency response of 40 Hz. Pressure was transduced by a strain-gauge manometer (SEM 482), the output being recorded on a multichannel ultraviolet recorder (SEM 3012). The common zero reference level for all pressures was set at 10 cm below the sternal angle and calibrated over the range 0 to 100 mmHg. Linearity of the manometers was checked before each study, and zero and calibration checks were made before and after each period of study. The left ventricular catheter was intermittently flushed from a reservoir with heparinised saline. The first derivative of left ventricular pressure (dP/dt) was computed continuously with an R–C differentiating circuit with a time constant of $4·7×10^{-3}$ mmHg/cm per s. A bipolar pacing catheter (USCI 5F United States Catheter Co.) was introduced through a right brachial vein and positioned at the junction of the superior vena cava and right atrium. Simultaneously with left ventricular pressure measurements, recordings were made of the electrocardiogram, phonocardiogram, and carotid arterial pulsations at a paper speed of 100 mm/second.

The electrocardiogram was recorded from adhesive-disc electrodes applied to each shoulder, the lower rib-cage, and the V_5 position, calibrated externally (1 mm=0·1 mV), and recorded on an ultraviolet recorder (SE Laboratories Model 3012). Lead II was employed for systolic time interval measurements.

A microphone (Siemen-Elema AB, Stockholm) was placed over the upper praecordium in the best position for recording the initial high frequency vibrations of the first and second heart sounds and connected to a preamplifier (SEM 4902). Recordings were made in a frequency band of 100 to 500 Hz.

The carotid arterial pulsation was recorded with a Philips Displacement Pick-Up 9310, which measured static and dynamic relative displacements, and connected to a Philips PT 1200 amplifier with a time constant of 1·0 s and a frequency range set at 0–100 Hz. Recordings were made with the head tilted towards the contralateral shoulder.

The obligatory requirements for recordings were a steady electrocardiographic baseline, sharp inscription of the initial vibrations of the first and second heart sounds, a sharp upstroke and clear incisural notch on the carotid arterial pulse tracing, and a clear atrial component of the left ventricular pressure measurements.

Studies were made at rest; control measurements were obtained after the patient had been lying quietly for 20 minutes. Atrial pacing was then started at increments of approximately 10 beats per minute to achieve a maximum of 140 to 160 beats per minute; pacing was discontinued with the appearance of any type of ectopic activity. Ten minutes later, isoprenaline was infused by means of a Harvard electromechanical pump (Model 901) in increments of 1 μg/minute every two minutes up to a maximum of 16 μg/minute (maximum heart rate 146 beats per minute). Twenty minutes later, 0·75 mg ouabain was given intravenously and measurements repeated at one, five, 10, 25, and 45 minutes.

LABORATORY TECHNIQUES, MEASUREMENTS, AND STATISTICAL ANALYSIS

Invasive techniques

First derivative of left ventricular systolic pressure (dP/dt) was calibrated in units of mmHg/s using a sinusoidal input. Measurements of the peak value, or dP/dt (max), were determined as the average of values recorded over 10 beats. Further, the instant in each cycle at which the intraventricular pressure exceeded end-diastolic pressure by 40 mmHg was determined. Hence, the common produced intraventricular pressure was 40 mmHg in every cycle. This determined level of intraventricular pressure was consistently below aortic diastolic pressure throughout each experiment. Average values of dP/dt recorded at this intraventricular pressure were again derived from 10 consecutive beats, and the ratio (dP/dt)/CPIP calculated at dP/dt divided by 40 mmHg. The ventricular end-diastolic pressure was measured at the nadir of the ventricular pressure recording after the atrial systolic increment.

Non-invasive techniques

The Q–S_2 interval (duration of electromechanical systole) was measured from the onset of ventricular depolarisation (Q wave) to the first high frequency vibration of the aortic component of the second heart sound. Left ventricular ejection time was measured from the beginning of the rapid upstroke to the trough of the incisural notch of the carotid arterial pulse tracing. Pre-ejection period was calculated by subtraction of left ventricular ejection time from Q–S_2: this interval corresponds with the beginning of ventricular depolarisation to the start of left ventricular ejection.

From the photographic records, time intervals were determined in milliseconds with the assistance of a D–MAC computer linkage, programmed to derive and print out heart rate, individual intervals, and their mean ± standard error for each selected series of heart beats. Series of 15 to 20 consecutive beats were selected, as it was found that a minimum of 12 individual beats was required before the observed mean value changed less than 3% with the addition of a further beat. Systolic time indices corrected for

heart rate[9] were also derived, but were not analysed in detail for reasons explained later.

Results

VARIATION IN SYSTOLIC TIME INTERVALS IN NORMAL SUBJECTS (Table 1)

In all four normal subjects there was considerable day-by-day variation in heart rate and systolic time intervals, despite the fact that they were entirely familiar with the procedure and that the measurements were made at the same time each day and under identical laboratory conditions. Moreover, there was little within-subject correspondence between changes in heart rate and duration of electromechanical systole (Q–S_2), ejection phase, or pre-ejection time. There was an inverted relation between changes in heart rate and directional changes in systolic time intervals at some point in each subject.

Table 1 *Within-subject variation in uncorrected systolic intervals recorded at 09.30 am on separate days*

Subject	Heart rate	QS₂	LVET	PEP
H	70	394	302	92
	46	432	318	114
	63	432	322	110
F	72	374	283	91
	73	387	298	89
	61	389	299	90
	63	423	324	99
M	56	393	326	67
	53	422	341	81
	65	398	306	92
P	68	393	290	103
	68	395	301	94
	72	369	294	75
	75	370	295	75

CORRELATION BETWEEN DIRECT AND NON-INVASIVE METHODS OF MEASUREMENT OF RATE OF RISE OF LEFT VENTRICULAR PRESSURE DURING SYSTOLE IN PATIENTS

Control values

At rest, dP/dt (max) and (dP/dt)/CPIP averaged 1219±121 mmHg/s and 25±2·1 s, respectively.

Neither variable showed any between-subject relation to heart rate (range 71 to 90 beats/min). Left ventricular end-diastolic pressure was 11±1·5 mmHg. Simultaneous measurements of Q–S_2, left ventricular ejection time, and pre-ejection period were 380±5, 284±5, and 96±5 ms, respectively.

Atrial pacing (Table 2)

During atrial pacing there was a tendency to reduction in left ventricular end-diastolic pressure and a stepwise increase in dP/dt (max) and (dP/dt)/CPIP in almost all subjects. There was a predictable linear relation between the increase in paced heart rate and both of the latter measurements (Fig. 1 and 2).

Q–S_2 and left ventricular ejection time were both consistently reduced in all subjects with increase in paced heart rate, and there was a predictable linear relation between heart rate increment and both

Table 2 *Changes during atrial pacing*

| Case No.	Rate	LVEDP	dP/dt(max)	(dP/dt)/CPIP	Q–S₂	LVET	PEP
1	66				384	286	98
	99				339	239	100
	107				330	228	102
	115				328	207	121
2	81	16	1299	28·9	344	267	73
	102	16	1477	29·3	328	242	87
	106	14	1460	31·2	326	237	89
	123	14	1831	34·3	287	212	75
	130	12	1801	37·5	284	204	80
3	78	12	1035	20·4	381	306	75
	88	13	1222	21·1	358	273	85
	122	12	1428	25·0	313	233	80
	134	12	1460	27·6	302	216	86
4	72	16	880	24·1	394	291	103
	96	14	1260	28·8	365	264	101
	122	12	1642	36·0	338	234	104
	140	12	1908	41·5	315	213	102
5	77	8	836	16·0	378	266	112
	86	7	906	16·8	371	264	106
	99	8	1009	18·7	357	250	107
	109	4	1260	22·4	354	251	103
	123	4	1269	20·6	326	226	100
	132	4	1052	19·6	320	217	103
	141	4	1113	24·7	314	214	100
	161	4	1571	31·0	294	190	104
6	86	7	1413	23·9	398	281	117
	91	4	1700	29·5	373	270	103
	98	6	1860	38·2	374	263	111
	114	4	1573	40·5	339	241	98
	123	9	2950	52·4	324	226	98
	133	—	3106	54·5	313	214	99
	145	4	3200	54·6	300	193	107
	149	—	3000	—	291	183	108
7	62	8	1462	29·3	413	306	107
	87	6	1672	29·0	360	265	95
	91	5	1761	29·4	361	262	99
	114	4	1920	30·3	333	242	90
	125	4	1922	32·0	324	234	91
	131	3	2039	30·7	315	225	91
	141	—	—	—	314	205	110
8	76	12	1613	32·1	387	311	75
	82	12	1857	36·3	375	305	70
	94	10	2035	38·0	365	295	70
	106	10	2228	42·5	341	274	67
	109	10	2315	44·0	340	268	72
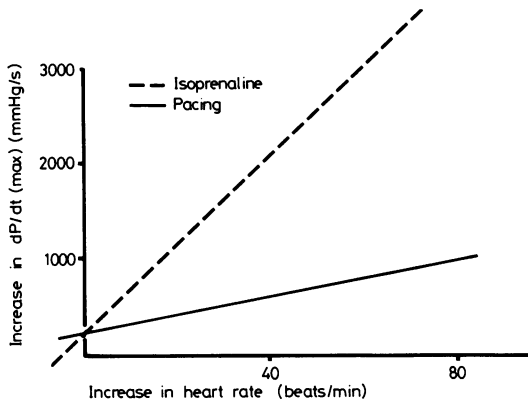
Fig. 1 *Comparison of group regression lines relating increases in dP/dt(max) and heart rate during atrial pacing and isoprenaline infusion.*

Fig 3 *Comparison of group regression lines relating decrease in QS$_2$ with increase in heart rate during atrial pacing and isoprenaline infusion.*

variables (Fig. 3 and 4). There was no consistent change in pre-ejection period in any of the eight subjects during pacing increase in heart rate (Fig. 5).

Isoprenaline infusion (Table 3)
Infusion of isoprenaline was associated with increases in heart rate of 41 to 65 beats per minute in six subjects, but in two others the maximal heart rate increases were 9 and 17 beats/min despite an infusion rate of 12 μg/min. In all subjects there was a consistent stepwise reduction in left ventricular end-diastolic pressure together with a stepwise increase in dP/dt (max) and (dP/dt)/CPIP. There was a significant linear relation between the increase in heart rate and both of the latter measurements, the changes after isoprenaline being significantly greater
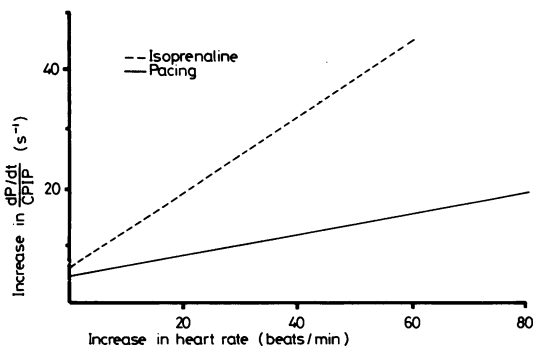
than those associated with pacing-induced increases in heart rate (Fig. 1 and 2).

Likewise the reductions in Q–S$_2$, left ventricular ejection time, and pre-ejection period at given increases in heart rate were significantly greater after isoprenaline than during pacing (Fig. 3, 4, and 5).

Table 4 compares the regression relations between changes in these variables and increases in heart rate. In each case, the regression slope was significantly greater for isoprenaline than for pacing-induced increases in heart rate.

Fig. 2 *Comparison of group regression lines relating increases in (dP/dt)/CPIP and heart rate during atrial pacing and isoprenaline infusion.*
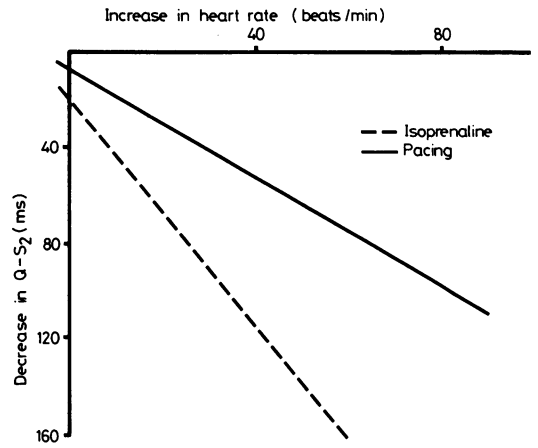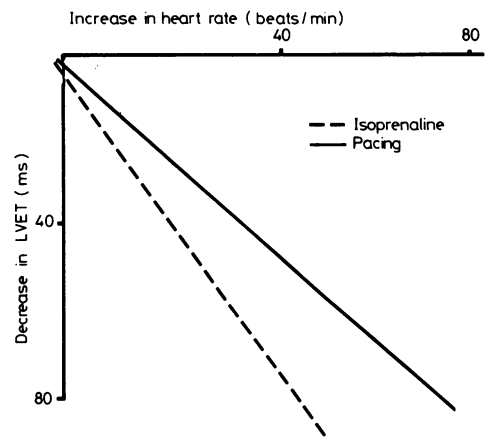

Fig. 4 *Comparison of group regression lines relating decrease in LVET with increase in heart rate during atrial pacing and isoprenaline infusion.*
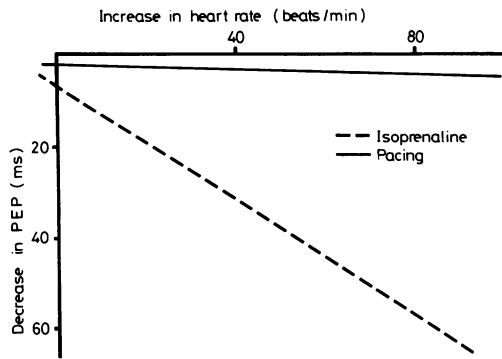
Fig. 5 *Comparison of group regression lines relating decrease in PEP with increase in heart rate during atrial pacing and isoprenaline infusion. The regression slope for atrial pacing does not significantly differ from zero.*

Ouabain (Table 5).

Maximum increases in cardiac activity occurred between 10 to 25 minutes after the injection of ouabain. At this time there was a reduction of seven to 21 beats/min in six patients, but no change in heart rate in two. Changes in left ventricular end-diastolic pressure did not exceed 2 mmHg in any subject. There was an average maximum increase in dP/dt (max) and (dP/dt)/CPIP of 41% and 29%, respectively. Simultaneously, reductions in left ventricular ejection time of 6 to 30 ms and in Q–S$_2$ of 14 to 35 ms were measured in six patients. In one patient left ventricular ejection time and Q–S$_2$ were unchanged and in one the relation was reversed. Reductions in pre-ejection period (0 to 14 ms) were small and inconsistent.

Rate-independent changes

It was assumed that the inotropic component of an isoprenaline-induced change equalled the difference between values recorded at the same heart rate during pacing and during isoprenaline infusion. This measure was termed the rate-independent rise for dP/dt (max) and (dP/dt)/CPIP, and the rate-independent reduction for Q–S$_2$ and LVET. As the regression relation between each variable and electrically induced change in heart rate varied between individual patients, rate-independent changes were calculated separately for each patient.

For ouabain, rate-independent changes were calculated after extending the regression relation between each variable and paced heart rate to the lower heart rates recorded after ouabain.

Excellent correlations were shown within the patient group between the various rate-independent changes induced by drugs. For isoprenaline, rate-independent reduction in Q–S$_2$ correlated well with

Table 3 *Effects of isoprenaline*

Case No.	Rate	LVEDP	dP/dt(max)	(dP/dt)/CPIP	Q–S$_2$	LVET	PEP
1	72				374	263	111
	88				324	245	78
	68				330	258	72
	89				268	210	58
2	81	16	1271	25·6	355	272	84
	90	13	1619	33·5	320	257	63
	98	13	1872	35·8	298	249	50
	106	12	2418	48·1	263	225	37
	115	12	2535	49·3	254	219	35
	130	10	2740	51·7	221	185	36
	146	9	2876	53·8	208	179	29
3	77	15	1100	20·1	376	290	87
	81	11	1353	22·6	358	280	78
	85	9	1640	29·7	332	275	57
	86	8	1524	27·9	317	269	48
	86	8	1968	31·2	295	254	41
4	71	17	1243	26·5	383	300	83
	80	14	2068	39·1	334	270	64
	91	10	2863	48·2	289	243	46
	96	7	3172	50·5	288	234	53
	110	5	3628	52·9	257	215	42
	114	5	3697	51·7	255	205	50
5	77	8	880	16·0	387	265	112
	94	6	1026	20·0	347	263	85
	103	4	1628	31·4	308	222	86
	112	5	1972	37·2	283	194	90
	121	4	2000	38·3	272	197	75
6	95	8	1700	30·9	375	264	111
	99	10	2203	47·1	346	255	91
	106	6	2680	42·6	315	237	78
	112	3	3305	45·1	301	235	66
	128	—	—	—	277	202	75
	132	—	3940	—	275	196	79
	140	6	4604	73·7	259	188	71
7	80	8	1456	29·3	379	283	97
	92	8	1598	32·5	357	258	99
	108	4	2672	43·5	303	234	69
	110	3	3414	55·4	283	222	61
	129	2	4207	61·2	253	197	56
	138	2	4405	65·0	237	182	55
8	78	12	1612	32·1	390	311	79
	84	8	2062	38·6	346	276	70
	98	6	2622	50·6	313	265	48
	106	6	2893	57·1	280	236	44
	119	6	4689	71·2	247	200	48

rate-independent rise in dP/dt (max) (r=−0·68, p<0·001) and in (dP/dt)/CPIP (r=−0·75, p<0·001), and rate-independent reduction in left ventricular ejection time was also well correlated (r=−0·68, p<0·001) for both dP/dt (max) and (dP/dt)/CPIP. For pooled data from both isoprenaline and ouabain experiments the correlations were highly similar to the above values for isoprenaline alone. As shown in

Table 4 *Regression formulae relating change in heart rate (x) with change in other variables (y) in a group of eight patients*

	Atrial pacing	Isoprenaline
dP/dt(max)	y=250+9·5x	y=247+45·9x
(dP/dt)/CPIP	y=4·5+0·19x	y=6+0·66x
QS$_2$	y=−7−1·13x	y=−23−2·33x
LVET	y=−4−1·12x	y=−7−1·71x
PEP	y=−2−0·02x	y=−6−0·64x

Fig. 6, the true relation between rate-independent changes in dP/dt (max) and Q–S$_2$ appeared curvilinear over a wide range of isoprenaline induced effects. Over the smaller range of effects induced by ouabain alone, lesser degrees of correlation were observed. As illustrated in Fig. 7, there was no significant correlation between rate-independent changes in Q–S$_2$ and dP/dt (max) (r=−0·34,

Table 5 *Effects of ouabain at various times (min) after injection*

| Case No.	Min	Rate	LVEDP	dP/dt(max)	(dP/dt)/CPIP	Q–S$_2$	LVET	PEP
1	0	69				380	273	101
	10	62				362	263	100
	25	60				368	271	97
2	0	83	14	1237	28·9	355	261	77
	10	81	12	1439	27·9	333	260	73
	25	83	13	1525	30·4	332	259	73
	45	82	12	1590	32·4	326	255	71
3	0	75	12	997	20·4	381	299	94
	10	57	10	1103	20·9	406	318	88
	25	54	9	1225	21·4	410	322	88
4	0	70	13	879	24·1	403	284	110
	10	63	13	1126	23·1	402	296	106
	25	64	11	1212	26·2	376	285	90
5	0	78	8	836	16·0	388	280	108
	10	62	9	1029	19·2	391	272	118
	25	64	8	1127	14·3	387	290	97
	45	62	10	960	19·0	391	282	109
6	0	90	7	1413	23·9	377	280	105
	10	95	8	2404	47·8	351	256	94
	25	88	8	2011	42·9	365	257	108
	45	94	8	2008	43·9	353	250	103
7	0	81	8	1556	29·3	377	283	100
	1	84	8	2120	36·4	364	270	94
	5	67	10	2043	35·7	386	292	94
	10	70	8	2136	37·7	376	284	92
	25	70	8	2058	37·8	363	275	88
	45	72	8	1912	35·9	365	266	99
8	0	76	10	1613	32·1	387	309	70
	1	68	10	2281	34·0	380	291	88
	5	65	10	2393	37·9	382	299	83
	10	73	10	2537	42·0	365	297	69
	25	70	10	2322	40·7	365	293	72
	45	75	8	2212	40·6	352	281	71
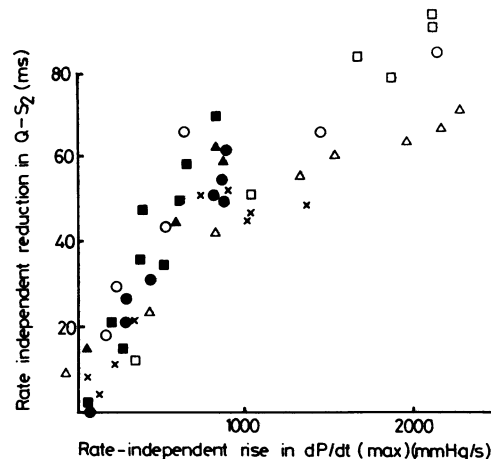
Fig. 6 *The relation between rate-independent changes in QS$_2$ and dP/dt(max) induced by isoprenaline. Each point represents values obtained at one infusion rate in one patient. All results from one patient are indicated by the same symbol.*

p>0·05),· and rate-independent reduction in left ventricular ejection time showed only a modest correlation with dP/dt (max) (r=−0·44, p<0·05). As opposed to isoprenaline effects, however, rate-independent changes in dP/dt (max) after ouabain were only moderately correlated with (dP/dt)/CPIP (r=0·45, p<0·05), and for the latter there were better correlations (r=0·57, p<0·01) with ouabain-induced rate-independent reductions in both Q–S$_2$ and left ventricular ejection time.
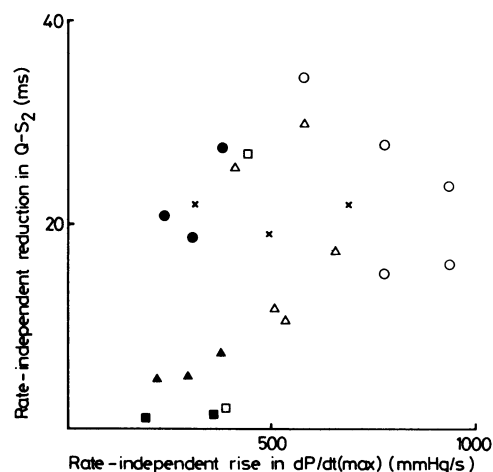

Fig. 7 *The relation between rate-independent changes in QS$_2$ and dP/dt(max) induced by ouabain. Each point represents values obtained at one particular time after ouabain administration, and results from one patient are indicated by the same symbol.*

Discussion

The difficulties in deriving a reliable measure of myocardial contractility in intact man have been reviewed by Mason *et al.*[10] Though there is no completely satisfactory method, it is generally accepted that measures derived from the rate of change of intraventricular pressure correlate well with contractility under most experimental conditions.[1-3] However, dP/dt (max) responds not only to change in contractility, but also to alteration in either the preload or afterload of the ventricle. In the left ventricle, preload and afterload are reflected by left ventricular end-diastolic pressure and aortic mean systolic pressure, respectively. With drugs such as isoprenaline which raise aortic systolic and reduce diastolic pressure, (dP/dt)/CPIP may be a more accurate measure of contractility, as it is independent of aortic blood pressure and is also unaffected by moderate changes in left ventricular end-diastolic pressure.[11] This measure must be recorded during isovolumic systole, dP/dt being determined at any selected level of developed pressure common to control and intervention conditions. Like dP/dt (max) it is responsive to change in heart rate. The major limitation of either measure, however, is that they require cardiac catheterisation, and therefore cannot be used for studies of more than short duration, or in studies comparing the effects of several compounds or doses.

Determination of the duration of systole is a much more convenient procedure, is completely safe, and has been reported to provide a sensitive measure of change in cardiac performance.[4-6] Externally recorded durations have been shown to be valid. The left ventricular ejection time derived externally from a carotid tracing was an accurate reflection of recordings obtained simultaneously from fluid-filled catheters in the proximal aorta,[4 12 13] and high fidelity micromanometer tip catheterisation of the left ventricle confirmed the accuracy of the determinations of Q-S$_2$, left ventricular ejection time, and pre-ejection period derived externally.[14 15] There is evidence that certain pathological conditions specifically affect one or other phase,[4 16] though Parker and Just[17] failed to detect characteristic abnormalities even in the presence of severe derangement of ventricular performance. Like dP/dt (max), systolic intervals are dependent upon alteration in preload and afterload,[18 19] though the precise relation in intact man is more complex than in the isolated heart.[20]

Q-S$_2$, left ventricular ejection time, and pre-ejection period have been shown to be inversely related to heart rate in a group of healthy subjects with a wide range of resting heart rates.[9 21] The slopes of regression equations relating systolic intervals to

rate in these subjects were 2·1 to 2·4 for Q-S$_2$, 1·7 for left ventricular ejection time, and 0·4 for pre-ejection period. The authors have proposed that indices of systolic intervals corrected for rate according to these regression slope values are applicable measures of altered myocardial contractility. These regression slopes, however, are very similar to those derived after infusion of isoprenaline, a powerful stimulant of cardiac beta-adrenergic receptors. This suggests that the wide range of resting heart rates reported in the earlier studies was associated with individual variation in sympathetic drive. It follows that rate-corrected indices derived from such a population will correct for the total effects of altered adrenergic stimulation. Such indices are not applicable to studies of other factors changing contractility, as they consistently over-correct for heart rate increases. As would be expected, the published rate-correction indices have been reported to be insensitive measures of the inotropic effects of catecholamines.[22] When in our studies heart rate was increased by electrical pacing, significantly less shortening of systole was observed than predicted from the reported regression equations. Further, only the ejection phase of systole shortened. The relations of systolic intervals to altered heart rate are very similar during electrical pacing or after atropine administration.[23] Atrial pacing slightly reduces left ventricular end-diastolic pressure and also slightly increases aortic diastolic pressure,[24] and it is likely that these changes have some contributory effect upon systolic intervals. It seems reasonable, however, to attribute similar responses to the specific rate-increasing component of a drug's effect. Therefore, the regression equations relating systolic intervals to paced rate change appear more applicable to studies of drug effects than those based upon a range of resting heart rates.

No correction for drug-induced change in heart rate should be applied to pre-ejection period.[25] The fact that pre-ejection period appears to be rate-independent is a considerable advantage, but unfortunately this is offset by the fact that it is a small, derived variable, and is particularly prone to technical error in measurement. This may account for the insignificant reduction in pre-ejection period recorded after ouabain administration. It has been suggested that the ratio of pre-ejection period to left ventricular ejection time may be a more suitable measure of myocardial performance,[9] but this ratio appeared to be highly dependent upon rate change and increased substantially during electrical pacing. The interval of longest duration, Q-S$_2$, is least affected by the technical difficulties in accurate determination, but must be corrected for change in heart rate. It is suggested that calculated rate-independent change in Q-S$_2$ is the most reliable indicator of inotropic effect.

For the large changes produced by isoprenaline, there was an excellent inverse correlation for rate-independent changes in $Q-S_2$ and dP/dt (max). The non-significant correlation for ouabain represents the smaller number of experiments to some extent, but the technical imprecision in measurement is more important with a drug producing only small to moderate increase in contractility. Though systolic intervals are dependent upon preload and afterload, they correlated equally well with dP/dt (max) and (dP/dt)/CPIP, possibly because both drugs induce a small change in preload or afterload relative to the increase in contractility. Determination of rate-independent change in $Q-S_2$ appears to be a useful indication of moderate to large inotropic change induced by any drug which does not radically alter left ventricular end-diastolic pressure or aortic blood pressure. In studies of drug-induced inotropic effect, rate-dependent change in $Q-S_2$ can be calculated by multiplying the recorded change in heart rate by the factor $1 \cdot 13$ derived from the patient group (Table 4). Rate-independent change can be derived as the difference between the observed change in $Q-S_2$ and the calculated rate-dependent change. It is preferable, however, that individual rate-dependence factors should be derived, as they appeared to be unique for each subject. This could be accomplished by recording $Q-S_2$ at several heart rates after administration of atropine.

These adaptations of the techniques for determination of systolic intervals may provide a precise though not highly sensitive method of assessing the effect of drugs on myocardial contractility. The techniques are convenient enough to permit repetition. The observed degree of day-to-day variation in systolic intervals, however, probably reflects variation in the degree of sympathetic drive to the heart, and suggests that measurements would be valid only if recorded during a single day.

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