PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **180**, 303-311 (1985)

Cardiac Dynamics of the Langendorff Perfused Heart[1] (42180)

RENAUD TROUVE AND GABRIEL NAHAS

Laboratoire de Biophysique, Université Paris VII, INSERM U126, 75010 Paris, and College of Physicians & Surgeons, Columbia University, New York, New York 10032

Abstract. The Langendorff perfused heart is studied in a closed system with (i) automatic regulations to maintain constancy of the perfusion column (Krebs–Henseleit + 0.5% albumin or 25–30% washed erythrocyte suspension), (ii) continuous recording of rate, coronary flow, and supravalvular aortic pressure. A microcomputer with software interface is used for storage treatment and on-line analysis of the recorded variables. In 38 preparations perfused with Krebs–Henseleit, minimal diastolic (61.2 ± 2.8 mm Hg) is significantly below and peak systolic (98.7 ± 3.6 mm Hg) significantly above perfusion pressure (80 mm Hg). Pressure difference between minimal diastolic and peak systolic (ΔP) is 37.5 ± 1.8 mm Hg. Increases in perfusion pressure will be associated with increases of coronary flow and ΔP, which is also increased by isoprenaline administration. Oxygen consumption decreased by 76% when perfusion pressure was lowered from 80 to 60 mm Hg in hearts perfused with a 30% erythrocyte suspension. All of these experimental results were interpreted as indicating that ΔP measured in this system resulted from an ejected volume (x acceleration) from the heart. The ejected volume corresponds to a valvular leak caused by the rigid nature of the system which is devoid of aortic compliance. ΔP may be considered an index of left ventricular performance, an indication that the Langendorff preparation studied under the present conditions is a working heart. A 100-μl volume constant infusion syringe for time administration of cardioactive drugs may be inserted at the base of the perfusion column to obtain dose–response effects.

Langendorff described in 1895 (1) an isolated mammalian beating heart perfused in a retrograde fashion through the aorta by a column of Ringer lactate. This preparation constituted the first model to study the direct pharmacological action of different substances on the heart. However, heart rate was the only marker which could be measured with any consistency. "Force of contraction" or inotropic function and coronary flow were difficult to assess with consistency and precision. In subsequent years, coronary flow was approximately measured by sampling coronary outflow (2–4). Force of contraction of the myocardium was measured by one of the three following methods: by a strain gauge (5); by recording pressures from a fluid-filled balloon inserted into the ventricle (6); or by recording intraventricular pressure by means of a blunted needle inserted into the ventricle chamber (4). These three invasive methods yield only approximate results: the intraventricular balloon has to be filled to a different volume with each heart, and as a result there is significant dispersion of the results depending on the size of the heart; the balloon will distend the ventricle in early diastole and may therefore impede coronary flow in the subendocardial area (1). The strain gauge must be inserted surgically on the myocardial surface which results in some muscle damage (8). The recorded signals will also vary widely from one preparation to the next because of the difference in insertion and orientation of the gauge (9). While some authors recognized that "ventricular filling was occurring during diastole and that some fluid was ejected with systole (4), it was generally assumed that the Langendorff perfused heart was nonworking, e.g., contracting in an empty state, a conclusion which led some authors to introduce a fluid-filled balloon in the left ventricle to measure myocardial contractile force.

The present study was aimed at clarifying the dynamics of the cardiac function of the Langendorff perfused heart as it was originally described. For this purpose a new system was designed for continuous measurement of supra valvular aortic pressure, and coronary flow. This preparation was also designed for time

[1] This paper was presented in part at the 1985 FASEB meeting, Anaheim, Calif.

0037-9727/85 $1.50

administration of known amounts of cardioactive drugs to obtain dose–response effects. Finally, an instrument interface was designed and adapted to a programmed microcomputer for on-line storage, processing, and analysis of the data.

Methods. The system used in this study consists of the following components:

(1) modified Langendorff preparation comprising (Fig. 1) (a) an automatic regulation device to maintain volume constancy in a closed circuit perfusion system as described by Duruble *et al.* (10) and (b) recording equipment for continuous measurement of coronary flow, frequency, and supravalvular aortic pressures; and

(2) a microcomputer and a software interface for storage and treatment of the recorded variables. (See Appendix I.)

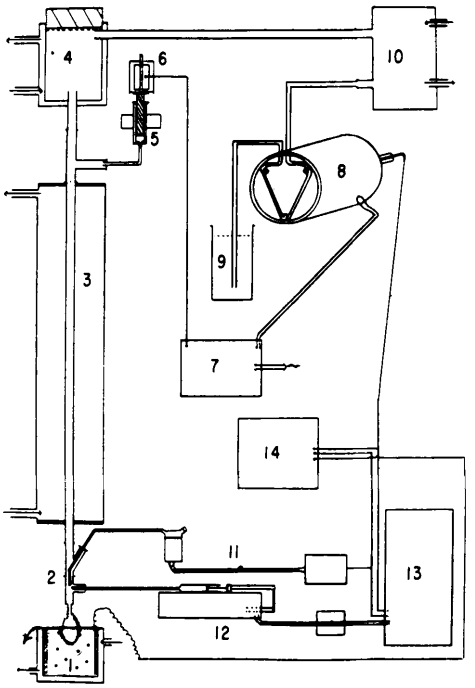


FIG. 1. Modified Langendorff perfused heart: (1) thermostated bath (constant level) with EKG electrodes (six pairs); (2) perfusion/cannulation system; (3) thermostated perfusion column; (4) thermostated filling reservoir (constant level); (5) floating syringe; (6) displacement transducer; (7) pump speed control triggered by displacement transducer; (8) modified pump with tachymeter; (9) perfusate reservoir; (10) membrane oxygenator; (11) pressure transducer; (12) electric precision syringe; (13) computer with cards and software; (14) chart recorder.

The Langendorff perfused heart. Fasting animals (rats, guinea pigs, or rabbits) maintained on *ad libitum* standard laboratory diet are anesthetized with ether. The heart is rapidly excised and placed in a beaker containing iced saline and heparin (11). The heart is then mounted on an aortic cannula at the base of the perfusion column. The heart is suspended over a saline-filled thermostated container; only the lower half of the heart is immersed in saline, to allow for gravity drainage of coronary output from the right auricle.

The fluid for retrograde perfusion of the heart is contained in a closed thermostated column (37°C). For routine pharmacological studies, the perfusion pressure is set at 80 mm Hg. In six preparations a different perfusion device was utilized which allowed for varying the range of perfusion pressure from 50 to 120 mm Hg (12). Such variations were performed by changing the height of the displacement transducer syringe, the plunger of which was filled in part with mercury (Fig. 2). In these instances, the entire perfusion system was placed in a glass cabinet thermostated at 37°C.

The perfusion fluid routinely used for pharmacological studies is a Krebs–Henseleit bicarbonate buffer containing 0.5% albumin. In selected experiments when oxygen uptake is to be measured, the perfusion system is filled with a 25 to 30% erythrocyte suspension in Krebs–Henseleit as described in a previous paper (11). The perfusion fluid is first equilibrated through a disposable membrane oxygenator (Cobe Pediatric) with a gas mixture containing 95% O_2 and 5% CO_2 when Krebs–Henseleit is used so as to afford maximal oxygenation, and avoid direct gas liquid interface which produces bubble formation and protein denaturation. The resulting pO_2 is 629 ± 30 mm Hg, pCO_2 20 mm Hg, and pH 7.4 ± 0.025. These variables are measured on an ABL1 radiometer.

A mixture of 20% O_2, 5% CO_2, and 75% N_2 is used to equilibrate the 25 or 30% erythrocyte suspension. Resulting pO_2 is 135 ± 5 mm Hg and pCO_2 35 ± 3 mm Hg.

Measurement of coronary flow. The entirely closed perfusion column is connected through a side arm to a syringe which continuously monitors the total filling pressure of the system. Any displacement of the plunger of the syringe is measured by a transducer (L. N. In-

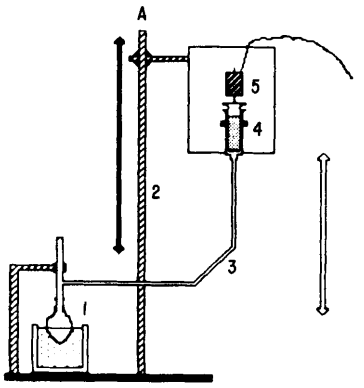


FIG. 2. Schematic representation of the system used to change perfusion pressure of a Langendorff perfused heart: (1) isolated perfused heart; (2) movable stand; (3) connecting side arm; (4) syringe with mercury-filled plunger (equal to 40 mm Hg); (5) displacement transducer. Black arrow represents the range of possible displacement of the perfusion pressure system. The white arrow represents the actual perfusion pressure plus Hg column in the plunger of the syringe.

dustry Senseline CX151) and transmitted to an amplifier so that any change in volume of the perfusion column is perceived by the syringe. The amplifier, in turn, triggers the motor of the pump. The volume lost from coronary outflow is immediately replaced and pumped from a reservoir through the oxygenator into the perfusion column where a constant volume is maintained. The inertia of the system is quite low which permits an excellent regulation of the volume of fluid in the column. The pump is a modified Masterflex Cole Palmer to which antivibratory devices and a precision tachymeter have been added. Its electrical input–output and controls have been modified to obtain the required on–off sequences and external control connections (10). The precision tachymeter continuously measures its output. There is a linear relationship between volume delivered by the pump and the signal transmitted by the tachymeter, which is carefully calibrated before each experiment. The maximal inertia of this system (essentially hydraulic) results in changes in volume of the perfusion column which do not exceed 200 μl. This volume "V" oscillates between V and $V - 150$ μl which represents approximately 1/85th of the average coronary outflow (in ml/min) of a rat heart perfused with Krebs–Henseleit. The feed back of the circuit is less than 1 sec. Such a system will reflect near instantaneous coronary outflow and may be integrated over 1 min in a fashion which is not matched by other methods of measurement. Pump output may be measured within ± 0.1 ml/min.

To this continuous measurement of coronary outflow another feature was added to perform dose–response curves required by pharmacological and toxicological investigations. A cannula with minimal dead space was inserted via a three-way stopcock into the rigid support to which the heart is suspended. This cannula is connected to a constant infusion syringe (Precidor Infors AG Basel) which is set to deliver its content (100 μl vol) during 1 min. Since the volume of coronary outflow is continuously recorded the molar concentration of the drug to be studied may be calculated according to

$$\text{molar concentration} = \frac{\text{weight of drug } (\mu\text{g in } 100\ \mu\text{l})}{\text{mol wt of drug} \times 10^3 \times \text{coronary flow in ml/min}}. \quad (1)$$

As the volume of drug injected is very small in relation to coronary outflow, it will not interfere with the latter.

Measurement of supraaortic pressures. Supraaortic pressures are recorded through a rigid catheter introduced by a "Y" tube into the perfusion column and connected to a strain gauge Hewlett Packard Sanborn 1280C (Fig. 1) and its free extremity is perpendicular to aortic outflow. The entire system: Y tube connection, stopcock for drug administration, aortic cannula, perfusion column, is rigid and identical for each preparation; it has a constant resistance and is devoid of compliance.

The pressure recorded at the end of the catheter oscillates between a minimum and a maximum which are a function of perfusion pressure. A multichannel variable speed and

fast response (0–10 Hz) recorder (Hellige Multiscriptor) is used to record pump output supraaortic pressures and electrocardiogram. A second recorder is also available to allow for simultaneous fast and slow speed recording. Rate is computed from pressure measurements. All of these measurements may be performed with the heart at rest or after administration of different drugs.

Measurement of oxygen uptake. Oxygen uptake of the Langendorff perfused heart was measured in six preparations all perfused sequentially at pressures of 60 and 80 mm Hg. O_2 content of coronary sinus (CVO_2) and arterial blood (CaO_2) was calculated according to the method of Defares and Visser (12):

$$CO2 = 3 \times 10^{-5}\, pO_2 \times C_{ap} \times s$$
$$= 3 \times 10^{-5}\, pO_2 \times C_{ap} \times (1 - e^{-\delta pO2})^2,$$

$CO2$ = O_2 concentration in liters of O_2/liters blood,

$pO2$ = partial pressure of O_2 in mm Hg,

s = % hemoglobin O_2 saturation,

C_{ap} = 1.34 × Hb concentration,

δ = 1.23/P50.

O_2 consumption of myocardium equals

$$VO_2 = Q(CaO_2 - CvO_2),$$

Q = coronary flow.

P_{50} of blood was measured with the instrument described by Duvelleroy *et al.* (13).

Microcomputer and software interface for storage and processing of recorded data. The described system is controlled and the resulting data processed by means of specially designed software and a microcomputer. Three parts comprise this system:

(i) An Apple II microcomputer with disk drive, text printer, and video-display for on-line analysis and processing of information.

(ii) Two A/D control cards. One for timing control with a slow acquisition ability of 50 a/sec. It controls the digital transfer of information with a parallel input–output to control the relays connected to the performing instruments (automatic infusing pump, recorders). The second card is a multichannel fast A/D converter (18250 a/sec) for data acquisition within a brief time frame (Interactive Microware).

(iii) External hardware for distribution of information with input to the computer and output to the equipment of the experimental preparation.

The software was designed for optimal performance of the available equipment, to ensure on-line acquisition and processing of data, as well as control of the external equipment and storage and analysis or modeling of acquired data. (See Appendix 1.)

Analysis of data. The analog to digital conversion of the physiological markers recorded by this system will give a greater precision than that of conventional recording methods. Under "controlled," stable conditions the reproducibility of coronary outflow, pressure, and rate measurements are better than ±1%. Therefore a variation in these measurements performed on the same preparation during its 1-hr period of stability and exceeding ±3% is significant ($P \leq 0.01$).

Results. Measurements of supraaortic pressures, rate, and coronary flow obtained during 90 min in a preparation perfused with Krebs–Henseleit are reported in Table I. Ten minutes following attachment of the heart to the base of the perfusion column, heart rate, coronary flow, and pressure measurements reach stable control values. During the following hour these measurements remain within ±1.5% of each other, and all pharmacological studies were performed within this time limit and with constant perfusion pressure.

TABLE I. CHANGES IN MEASURED VARIABLES OF AN ISOLATED HEART DURING 90 min FOLLOWING ITS ATTACHMENT TO THE PERFUSION COLUMN OVER PERFUSION PRESSURE = 80 mm Hg

Time (min)	Heart rate (beat/min)	Diastolic (mm Hg)	Systolic (mm Hg)	ΔP (mm Hg)	Coronary flow (ml/min)
0	289	60.3	99.7	39.4	20.3
10	261	61.4	98.9	37.5	13.4
15	258	62.1	98.5	36.4	13.6
30	255	61.4	99.0	37.6	13.4
45	255	61.4	98.8	37.4	13.4
60	263	61.7	98.2	36.5	13.6
75	265	61.5	98.7	37.2	13.4
90	272	62.8	96.8	34.0	11.8

Note. All pharmacological studies were performed between 15 and 75 min. "0" time marks the initial recording after heart has been attached to the system. Perfusion medium = Krebs–Henseleit. These are selected measurements as they appear on the printout after on-line analysis by the computer system. There is a printout of all variables every 30 sec.

Measurements performed on 38 hearts 10 min after attachment of the heart to the perfusion column were heart rate 237 ± 15 bpm, coronary flow 13.6 ± 2.5 ml/min, diastolic, systolic, and differential pressures (ΔP) 61.2 ± 2.8, 98.7 ± 3.6, and 37.5 ± 1.8 mm Hg, respectively. In three preparations, administration of isoprenaline 2×10^{-7} *M* significantly increased heart rate from 273 ± 18 to 342 ± 26 bpm, systolic pressure from 94 ± 3 to 128 ± 5 mm Hg, while diastolic pressure decreased from 64 ± 2.5 to 60 ± 2 mm Hg and ΔP increased from 30 ± 4 to 58 ± 5 mm Hg and coronary flow from 13.5 ± 1.4 to 14.6 ± 1.5 ml/min. Subsequent administration of propranolol 3×10^{-8} *M* decreased rate to 172 ± 12 bpm, ΔP to 13 ± 2 mm Hg, and coronary flow to control levels (Fig. 3).

In three studies, the hearts were perfused with a 25% suspension of washed erythrocytes in Krebs–Henseleit. In each experiment, supraaortic pressures followed the variations of perfusion pressure and so did ΔP and coronary flow. When perfusion pressure was increased from 83 to 116 mm Hg, diastolic pressure increased from 70 to 98 mm Hg, systolic from 98 to 135 mm Hg and ΔP from 29 to 37 mm Hg (Table II). Coronary flow increased from 5.2 to 10.0 ml/min. An increase in heart rate was also observed from 261 to 341 beats/min after the first increase in perfusion pressure.

In six studies the hearts were perfused with a 30% erythrocyte suspension in Krebs–Henseleit and perfusion pressures were changed from 80 to 60 mm Hg and back to 80 mm Hg. Oxygen uptake was a function of perfusion pressure: decreasing from 3.55 ± 0.55 to 0.82 ± 0.34×10^{-4} ml O_2/min/g wet wt/beat when perfusion pressure was lowered from 80 to 60 mm Hg and rising to 3.10 ± 1.20 mm Hg when perfusion pressure was restored to 80 mm Hg.

Discussion. The measurements of heart rate and systolic pressures observed in this study when the preparations were perfused with Krebs–Henseleit under a perfusion pressure of 80 mm Hg are comparable to those reported by other authors (4). Coronary flow was similar to those reported by others (2, 3) but below these reported by Neely *et al.* (4).

The consistent decrease in diastolic supraaortic pressure during diastole observed in this study was not reported by other authors probably because of the damping present in the perfusion system which they used (4). This pressure change suggested that ventricular filling was occurring during diastole. While supraaortic diastolic pressure fell below perfusion pressure with each diastole, peak systolic supraaortic pressure increased 18 to 19 mm Hg above perfusion pressure (Fig. 4). The magnitude of this positive pressure difference was similar to that of the negative pressure difference recorded during diastole (Fig. 4). As a result of these pressure changes, a differential pressure ΔP of the order of 34 to 37 mm Hg was recorded. (ΔP was increased by isoprenaline and decreased by propranolol, changes consistent with the known cardiac properties of these drugs (14, 15).)

Such pressure changes suggest that ventricular filling occurs during diastole and that some fluid is ejected with systole. It appeared that the fluid which filled the ventricle during diastole resulted from incompetent aortic

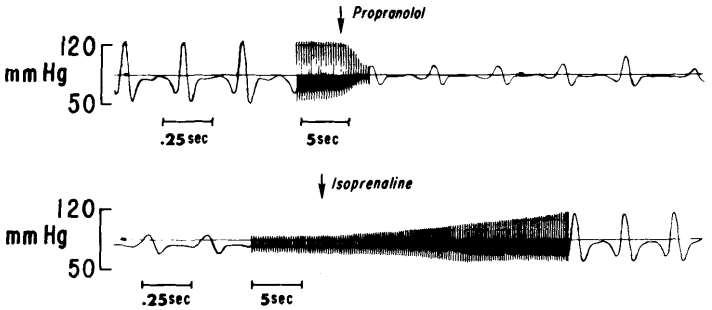


FIG. 3. Effect of propranolol 3×10^{-8} *M* and isoprenaline 2×10^{-7} *M* on the pulse pressure of the Langendorff perfused heart. (Perfusion pressure = 80 mm Hg.)

TABLE II. EFFECTS OF PERFUSION PRESSURE ON CORONARY FLOW AND ON RECORDED DIASTOLIC, SYSTOLIC, AND DIFFERENTIAL PRESSURE (ΔP) OF A MODIFIED LANGENDORFF PREPARATION[a]

	Perfusion pressure (mm Hg)	Time (min)	Diastolic (mm Hg)	Systolic (mm Hg)	ΔP (mm Hg)	Coronary flow (ml/min)	Rate (beat/min)
I	85	3	71	100	29	6.2	294
		4	70	98	28	6.1	293
		5	70	98	28	6.2	289
			(71.8)	(98.6)	(28.3)	(6.16)	(292)
II	85	14	71	98	27	5.2	254
		15	70	99	29	5.2	261
		16	69	99	30	5.1	264
			(70.0)	(98.6)	(28.6)	(5.16)	(260)
III	101	43	88	116	28	7.8	278
		44	88	115	27	7.9	334
		45	87	116	29	8.2	337
		46	86	117	31	8.2	338
		47	85	116	31	8.3	341
		48	85	117	32	8.3	341
			(86.5)	(116.2)	(29.6)	(8.1)	(328)
IV	116	49	99	134	35	10.0	330
		50	97	135	38	10.0	332
		51	99	135	36	10.0	332
		52	98	135	37	9.9	332
			(98.3)	(134.8)	(36.5)	(9.98)	(331.5)
V	58	53	46	70	24	4.2	333
		54	45	71	26	4.3	326
		55	45	70	25	4.3	336
			(45.6)	(70.3)	(25)	(4.26)	(331.6)
VI	86	56	71	102	31	7.0	328
		57	71	101	30	6.8	324
		58	69	99	30	6.6	333
			(70.3)	(100.6)	(30.3)	(6.8)	(330)

Note. Numbers in parentheses are the average of the figures taken during the outlined intervals. The first period (I) is one of stabilization after suspending the heart to the aortic cannula. In period II heart rate and coronary flow reach stable values (see text).

[a] Perfusion: 25% erythrocytes suspension in Krebs–Henseleit.

valves. Indeed Thebesian drainage could not account for ventricle filling: total Thebesian drainage represents at best 5% of coronary flow, of which 25% is drained in the left ventricle. With a coronary flow of 13 ml/min, left ventricular Thebesian drainage would amount to $13{,}000 \times 0.0125 = 160$ μl/min. Such a volume represents 1 stroke vol of the rat heart perfused with Krebs–Henseleit.

It was concluded that the Langendorff perfused heart was ejecting with each systole a stroke volume which leaked back into the heart during diastole, a mechanism already proposed by others (4). Such a mechanism was also validated in the preparation perfused with a 25% suspension of erythrocytes in Krebs–Henseleit: When perfusion pressure was increased from 85 to 115 mm Hg, diastolic pressure increased from 70 to 99 mm Hg and systolic pressure from 99 to 135 mm Hg, and pulse pressure from 30 to 37 mm Hg. Systolic and differential pressure fell back to 70 and 25 mm Hg, respectively, when perfusion pressure was lowered from 116 to 58 mm Hg. Coronary flow nearly doubled when perfusion pressure increased from 85 to 116 mm Hg. Under such conditions as reported by others (4) heart rate also increased. This increase in rate may be attributed (4) to an increase of the heat capacity of the coronary perfusate,

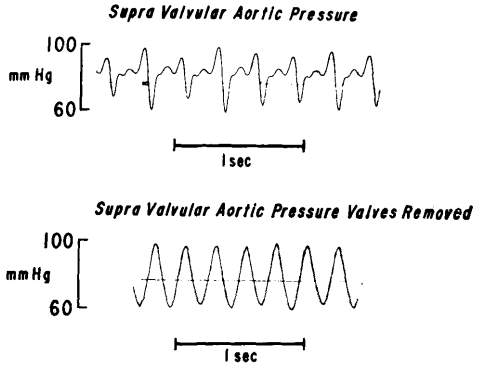


FIG. 4. Records from supravalvular catheter taken before and after aortic valves of the Langendorff perfused heart have been made totally incompetent by pushing back and forth the aortic cannula into the ventricle. (Perfusion pressure = 80 mm Hg.)

and an increased cardiac metabolism. Oxygen consumption decreased by 76% when perfusion pressure was lowered from 80 to 60 mm Hg in hearts perfused with 30% erythrocyte suspension in Krebs–Henseleit, reflecting decreased cardiac work.

All of the foregoing indicates that the differential pressure ΔP recorded by this system reflects an ejected volume (times acceleration) from the heart against the perfusion column. This volume corresponds to a valvular leak caused by the rigid nature of the system which is devoid of aortic compliance and presents a constant resistance. This valvular leak will become even more apparent when the aortic valves are made totally incompetent by pushing back and forth the aortic cannula into the ventricle. When this procedure is performed the pressure tracing will not present the notch corresponding to the rebound wave on the valves as the pressure equilibrates between ventricle and perfusion column. Instead, the pressure tracings oscillate in a sinusoidal fashion and the left ventricular chamber acts as a perfectly damped oscillator. (Fig. 4). Furthermore when a needle is inserted through the left ventricle, a pulsatile flow is observed as the heart ejects part of its content toward an area of pressure lower than that of the perfusion column. As a result there is a doubling of the recorded outflow from the system.

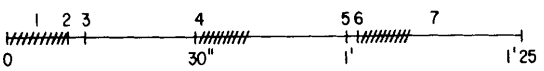
The measurement of differential pressure ΔP may be considered an index of left ventricular performance and contraction relaxation, an indication that the Langendorff preparation perfused under a pressure of 60 to 120 mm Hg, is a working heart. This experimental observation is validated by mathematical analysis (Appendix II).

The measurement of ΔP in conjunction with that of frequency and coronary flow continuously recorded and analyzed to test the effects or cardioactive drugs on the isolated heart represents a novel and useful method of investigation.

Appendix I: Computer processing of recorded data. The perfusion apparatus described in this study is controlled by an Apple II microcomputer and specially designed software. Two programs were designed: one for experiments lasting up to 9 hr allowing for processing and storage of information with continuous monitoring performed by two or three scannings per minute. Another for shorter studies, which will now be described.

Performance of software. Parameters are first determined to enable the computer to process information for final analysis, for instance, amount of drug in syringe to calculate molar concentration. The next phase determines acquisition of data in activating interface cards and selecting the number of channels and frequency of acquisition. During acquisition, the software processes recorded data, thus maximizing computer availability. Once data acquisition has ended, the computer processes the last data, stores it on a disk, prints it, and performs general calculations to compare different series of acquisitions.

In an experiment designed to test cardiac effects of a drug during 1 min, the external sequence is as follows (taking in account a 5- to 8-sec lag for the drug to reach the coronary vascular bed).



0: Interfaces activation and definition of acquisition parameters.
1: Start of acquisition of the control lasting 8 sec storage of results, start of control cards, onset of calculation of pressures, frequency, output.
2: Waiting 2 sec.

3: Triggering of the electric pump by starting the relay card, end of calculation of control data, storage on disk, printing, wait.
4: Start of first treated acquisition, processing of data, storage, print, wait.
5: Stop of perfusion by deactivation of relay card.
6: Start of last acquisition, calculation of parameters, storage, print.
7: General calculations and comparison with control, printing of final results.

Recorded parameters. Rapid acquisition card controls entry of signals into the computer according to a predetermined schedule.

For pressure signals, an acquisition of 640 points in 8 sec is sufficient to calculate the frequency with precision.

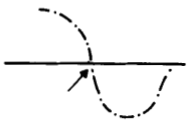
The treatment of these points is performed in four packs of 2 sec starting 2 sec following the start of acquisition (economy of calculation time). This allows for the measurement of maximal and minimum pressures corresponding to a mean of five samples of 40 points regularly spaced and then the selection of a threshold within the variations of the two extreme limits of maximal and minimal pressures which we define as "floating threshold." Its selection is set by the operator.

Frequency will be calculated by reexamining the 640 acquired points, and counting the number of passages of the wave form across the "floating threshold."

This method is quite effective and allows for the spontaneous variations in pressure since the "floating threshold" set by the operator will follow the mean changes of the pressure tracing, at the level set by the operator.

The number of intersections of the pressure wave forms with the "floating threshold" as well as the time of first and last intersection are known. Each measurement is calculated on the half period. Frequency is obtained by calculating the time period between first and last intersection and converting to 1 min the number of half periods computed in 8 sec.

The uncertainty of the timing of first and last intersection depends upon the height of the last pressure wave in relation to the "floating threshold."



The time period between two points being 0.0125 sec the error of time measurement is smaller than 0.0125×2 sec in 8 sec ($=0.0250/8$), of the order of 0.003 of a sec.

For a heart with a frequency of 240/min (4/sec) our system will detect 63 one-half periods during a time period of 7.875 sec $\pm$ 0.0250 or 63 one-half periods for a time period of 7.9 to 7.85:

$$\text{in one case, } \frac{63}{7.9} = 239.24/\text{min},$$

$$\text{in the other, } \frac{63}{7.85} = 240.76/\text{min}.$$

The resulting frequency will be given as 239 or 240/min.

A variation in frequency greater than ± 2 or 3 beats per min ($\pm 0.5\%$) (when the heart is beating at that rate) will therefore correspond to an actual frequency variation and not to an artefact of the computing system which has the performance ability to detect changes in rate of the order of $\pm 1\%$.

Variations in precision due to data processing of the system are still smaller.

Following this series of calculation, P_{max}, P_{min}, P_{mean}, and frequency are known.

During acquisition of the 640 points of pressure, the computer has recorded during 8 sec on another channel 128 points corresponding to the signals from the tachymeter of the pump which regulates volume replacement corresponding to coronary outflow. This represents 16 points/sec.

The average of all of these points will give a mean signal corresponding to mean outflow during 8 sec.

All of the parameters are printed and saved on disk or in memory for comparison with control.

Conclusion. Such a system has proven to be most useful for on-line acquisition, storage processing, and analysis of data obtained in

our experimental studies of cardioactive drugs. It possesses inner features of feasibility and flexibility which should make it most useful to study for dose-related pharmacological and toxicological effects of cardioactive drugs.

Appendix II: Mathematical Model. For a 40 mm Hg differential pressure (ΔP) to be recorded at the base of a catheter the force exerted on its surface must increase:

$$\Delta P = F/S.$$

The differential pressure recorded

$$\Delta P = P_1 - P_0$$

or

$$\Delta P = \frac{F_1 - F_0}{S}$$

if

$$\Delta P \neq 0, \quad F_1 \neq F_0 \quad (S \neq 0)$$

and ΔP represents a force related to cardiac performance assuming that in the equation $\Delta P = P_1 - P_0$. P_0 is an hydrostatic pressure and P_1 is an equilibrium pressure during the time fraction dt corresponding to $dp/dt = 0$ so that Pascal's law for a hydrostatic system becomes a particular case of Bernouilli general principle and assuming that F_1 is a mean value related to P_{im}. $P_{im} = (t_2/t_1)Fdt$ (impulsion law) applied to the heart.

When the heart is in diastole, the pressure P_0 is $P_0 = \text{pgh} + m_e(d^2x/dt^2)\,(1/S)$.

In diastole, there is no cardiac ejection, acceleration is zero and $(d^2x_0)/(dt^2) = 0$ and $m_e = 0$.

When the heart is in systole, pressure P_s is $P_s = \text{pgh} + m_e(d^2x/dt^2)(1/S)$. Acceleration given to the volume is no longer zero and the maximal recorded pressure should correspond to the maximal acceleration given to this ejected volume:

$$\Delta P = P_0 - P_1$$

$$= \text{pgh} - \text{pgh} + \left(m_e \frac{d^2x_0}{dt^2} - m_e \frac{d^2x}{dt^2}\right)\frac{1}{S}.$$

This equation indicates that ΔP is proportional and related to cardiac performance, e.g., to a force exerted by the heart. In the present system which is rigid, devoid of aortic compliance, and presents a constant resistance, ΔP should also be considered as an index of myocardial function and contraction-relaxation. This theoretical analysis is validated by the experimental data recorded in the present study which indicates that the measured supraaortic ΔP corresponds to an ejected volume from the heart (times acceleration).

1. Langendorff O. Untersuchungen am uberlebenden Saugethierherzen. Arch Ges Physiol (Pfluger) **61**:291–332, 1895.
2. Gus A, Kurland GS, Stone Freedberg A. Relation of coronary flow to oxygen supply. Amer J Physiol **199:** 179–182, 1960.
3. Willebrands AF, Van Der Veen KJ. Influence of substrate on oxygen consumption of isolated perfused rat heart. Amer J Physiol **212**(6):1529–1535, 1967.
4. Neely JR, Liebermeister H, Battersby EJ, Morgan HE. Effect of pressure development on oxygen consumption by isolated rat heart. Amer J Physiol **212**:804–814, 1967.
5. Cotten M de V. Direct measurement of changes in cardiac contractile force. Amer J Physiol **174**:365, 1953.
6. Bunger R, Haddy FJ, Querengasser A, Gerlach E. An isolated guinea pig heart preparation with in vivo like features. Pflugers Arch **353**:317–326, 1975.
7. Fulton WFM. Morphology of the myocardial microcirculation in microcirculation of the heart. Theoretical and Clinical Problems. Berlin/Heidelberg/New York, Springer Verlag, pp15–25, 1982.
8. Heethaar RM, Pao YC, Ritman EL. Cardiac function, fiber shortening and dynamic geometry. Comput Biomed Res **10**:271–285, 1977.
9. Hefner LL, Sheffield LT, Cobbs GC, Klip W. Relation between mural force and pressure in the left ventricle of the dog. Circ Res **11**:654–663, 1962.
10. Duruble M, Duvelleroy M, Gauduel Y, Martin JL, Teisseire B. Transient responses of coronary flow in the blood pressure rat heart submitted to changes in oxygen content. J Physiol **358**:321–334, 1985.
11. Stucker O, Trouve R, Vicaut E, Charansonney O, Teisseire B, Duruble M, Duvelleroy M. Effects of different hematocrits on the isolated working rabbit heart reperfused after ischemia. Int J Microcirc Clin Exp **2:** 325–335, 1983.
12. Defares JG, Visser BF. On the form of the physiological CO2 dissociation curve, the physiological O2 dissociation curve, and the diffusion curves of O2 and CO2 along the capillary path. Ann NY Acad Sci **96:** 21–31, 1962.
13. Duvelleroy M, Buckles R, Rosenkaimer S, Tung C, Laver M. An oxyhemoglobin dissociation analyser. J Appl Physiol **28**:227–233, 1970.
14. Robin E, Conan C, Puri P, Ganguly S, DeBoyrie E, Martinez M, Stock T, Bing RJ. A comparative study of nitroglycerin and propanolol. Circulation **36**:175–186, 1967.
15. Allwood MJ, Cobbold AF, Ginsbury J. Peripheral vascular effects of noradrenaline, isopropylnoradrenaline and dopamine. Brit Med Bull **19**:132–136, 1963.

Received January 25, 1985. P.S.E.B.M. 1985, Vol. 180.
Accepted June 17, 1985.