Lignocaine: effects on coronary blood flow in patients with recent myocardial infarction

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The myocardial clearance of rubidium may be obtained by praecordial counting after a single intravenous injection of Rb⁸⁶Cl. Eight patients with a recent myocardial infarction had this determination performed before and 5 minutes after the intravenous injection of 100 mg lignocaine. The average myocardial clearance of Rb was 45 ± 26 ml/min per 100 g myocardium before lignocaine. This compared to the normal value in our laboratory of 72 ± 21 ml/min per 100 g. After lignocaine the average myocardial clearance rose to 76 ± 32 ml/min per 100 g myocardium. The explanation of this finding as well as possible clinical applications are presented.

Lignocaine is an effective antiarrhythmic agent. It is the most widely used drug in the management of ventricular tachycardia and ventricular ectopic beats occurring as complications of acute myocardial infarction (Frieden, 1965; Gianelly *et al.*, 1967). Many investigators have shown that in therapeutic doses lignocaine does not cause significant alterations in cardiac output, stroke volume, or mean arterial pressure in patients with an acute myocardial infarction (Stannard, Sloman, and Sangster, 1968; Rahimtoola *et al.*, 1971). In spite of the apparent value of the drug, there is no information on its effects on coronary blood flow in man.

Recently, Donato, Bartolomei, and Giordani (1964) and Donato *et al.* (1966) have described a simple, relatively non-invasive technique for measuring coronary blood flow. This method uses radioactive rubidium and external counting. The major advantage of this technique is the avoidance of coronary sinus or coronary artery catheterization which enhances the practical value of this method. The procedure is, therefore, without hazard to the patient and the equipment required for the performance of the test is in most well-equipped radioisotope laboratories.

Another advantage of this technique is that the entire measurement may be completed in 90 seconds as compared to the time-consuming N₂O or ¹³¹I antipyrine method.

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The following study uses this isotopic method, and examines the effects of lignocaine on the coronary blood flow in patients with recent myocardial infarctions.

Methods

The praecordial counting was performed with a 5 × 5 cm NaI(Tl) scintillation detector with a lead collimator, 150 mm long with an external diameter 110 mm. Pulses from the detector were fed via a pulse height analyser to a digital ratemeter and then to a recorder. For ¹³¹I activity the pulse height analyser was set for the 364 KeV photopeak with a 100 KeV window. For ⁸⁶Rb, the pulse height analyser was set for 1.08 MeV with a 100 KeV window. The ratemeter time constant was set at 4 seconds for recording background and at 4 seconds during the procedures. The chart speed was set at 3 cm per minute. Blood activity was measured in a 5 cm well-type scintillation detector with the pulse height analyser setting as described for external counting of ¹³¹I and ⁸⁶Rb.

The counts are corrected for the relative inefficiencies in the *in vivo* and *in vitro* systems, introducing a coefficient $\bar{n}$ calculated from the counting rates obtained when two 500-ml flasks containing known concentrations of ¹³¹I and ⁸⁶Rb are counted externally under a standard geometrical arrangement.

$$\bar{n} = \frac{(\text{c.p.m./ml})^{131}\text{I (well)} \times \text{c.p.m. }^{86}\text{Rb (flask)}}{(\text{c.p.m./ml})^{86}\text{Rb (well)} \times \text{c.p.m. }^{131}\text{I (flask)}} \dots (1)$$

Experimental procedure

The experiments were performed in the morning on resting subjects in the supine position. A Cournand

cannula was introduced into the right brachial artery. The detector was positioned over the centre of the heart silhouette.

15 μCi of ^{131}I as radioactive iodine labelled human serum albumin in 0.5 to 1 ml saline, were then rapidly injected into the left cubital vein. Thirty seconds after the injection the praecordial counting and arterial blood sampling were started; both counting and blood sampling lasted 3 minutes and the rate of withdrawal was 1 ml every 4 seconds.

Within 5 minutes, 150 μCi of ^{86}Rb as rubidium chloride in 0.5 to 1 ml saline were rapidly injected into a cubital vein. Praecordial counts and arterial blood were taken as previously done after the RIHSA injection.

100 mg of lignocaine was given as bolus, intravenously. Five minutes after the drug administration, the radioisotope studies using ^{131}I and ^{86}Rb were repeated as described above. Care was taken to maintain the detector in the same position.

The blood pressure and cardiac rate were obtained before and after the lignocaine administration.

Calculations

The myocardial clearance (MCR) for ^{86}Rb was calculated in two steps:

(1) Calculation of the fraction F of the praecordial counting rate due to myocardial activity:

$$F = \frac{{}^{\text{Rb}} - \bar{n}\text{WB}\bar{\text{a}}\text{Rb}}{{}^{\text{Rb}}} \quad (1)$$

$$\text{where: } \text{WB} = \frac{{}^{\text{RIHSA}}}{\bar{\text{a}} \text{ RIHSA}}$$

and ${}^{\text{RIHSA}}$ and ${}^{\text{Rb}}$: net number of counts collected

on the scaler from 30 to 90 seconds after the injection of RIHSA and Rb, respectively; $\bar{\text{a}}$ RIHSA and $\bar{\text{a}}$ RB: radioactive concentrations per millilitre of arterial blood sampled from 30 to 90 seconds after the injection of RIHSA and rubidium, respectively; $\bar{n}$: the relative counting efficiency defined in equation 1. (2) Calculation of the myocardial clearance of rubidium (MCR) from the praecordial trace (Fig.):

$$\text{MCR} = \frac{D_f \cdot F \cdot 60 \cdot 100}{\int_0^\infty {}^{\text{Rb}}(t) dt}$$

where D_f = average net deflection mm of the ratemeter trace from 30 to 90 seconds.

FIG. Calculation of myocardial clearance of rubidium (MCR) from the praecordial tracing (see text). The area under the radiocardiographic curve is calculated after semilogarithmic extrapolation of the final downslope. D_f , the average deflection above background from 30 to 90 seconds after injection. (Reproduced from Gould et al. (1972)—British Heart Journal, 34, 815.)

TABLE Results in acute myocardial infarction group

Patient's age, sex, and condition	Experimental state	F%	Myocardial clearance of Rb (ml/min per 100g)	Blood pressure (mmHg)	Heart rate (beats/min)
62, M, inferior wall myocardial infarction (12 days old)	Control	20.0	20.0	110/75	80
	Lignocaine	50.0	46.0	125/90	96
40, M, inferior wall myocardial infarction (11 days old)	Control	40.0	42.0	110/70	68
	Lignocaine	52.0	93.0	110/75	68
65, F, inferior wall myocardial infarction (17 days old)	Control	40.9	66.8	95/50	76
	Lignocaine	82.4	145.0	100/50	80
58, M, anterior wall myocardial infarction (13 days old); temporary transvenous pacemaker because of complete heart block	Control	10.0	9.02	140/85	80
	Lignocaine	58.0	67.0	158/100	80
62, M, inferior wall myocardial infarction (35 days old)	Control	58.0	55.5	124/90	104
	Lignocaine	58.0	53.2	130/90	104
63, F, inferior wall myocardial infarction (10 days old)	Control	62.0	88.0	130/95	104
	Lignocaine	57.0	54.0	150/95	104
76, F, inferior wall myocardial infarction (10 days old)	Control	28.0	27.6	120/80	100
	Lignocaine	62.0	64.0	115/80	88
70, M, inferior wall myocardial infarction (13 days old)	Control	58.0	52.7	120/90	92
	Lignocaine	69.0	81.5	115/85	96
Mean	Control	39.6 $\pm$ 19.2	45.2 $\pm$ 25.9	119/79	88
	Lignocaine	61.1 $\pm$ 10.4	75.5 $\pm$ 32.1	125/84	90
	P value	NS	<0.05	NS	NS

Suitable radiation dosimetry measurements were considered in terms of the administered radionuclide dose to the target organ, critical organs, and total body dose. The patients received an integral dose in the order of 2.0 rad after the administration of the two ^{86}Rb injections and the two RIHSA injections. Based on these measurements ^{86}Rb could only be administered to the individual patient on two occasions.

Subjects

Five men and three women were studied. From clinical, laboratory, and electrocardiographic data it was deduced that they all had sustained a recent transmural myocardial infarction. Pathological Q waves of at least 0.04 sec in duration as well as a rise in the serum creatine phosphokinase, serum glutamic oxaloacetic transaminase, and lactic dehydrogenase were present in every case. The study was performed an average of 15 days after the infarction. No patient was studied less than 10 days after the infarction. At this time all of the subjects were clinically stable without evidence of congestive heart failure or arrhythmias. Patients were not studied within the first few days of the myocardial infarction, because of the potential dangers in transporting them to the isotope laboratory. In addition, an unstable clinical state could profoundly alter the coronary blood flow values. The clinical information on the entire group is listed in the Table.

The procedure was explained in detail to the subjects and the investigative nature of the study was stressed; informed consent was then obtained from all the patients.

Results

Complete data on the 8 patients are presented in the Table. The average value of the myocardial fraction of the praecordial counting rate (F) in the subjects studied with ^{86}Rb was 39.6 ± 19.2 per cent. The myocardial clearance of rubidium averaged 45.2 ± 25.9 ml/min per 100 g myocardium.

Effect of lignocaine

In 6 of the 8 cases with a recent myocardial infarction, the myocardial clearance increased after lignocaine, the rise ranging from 26 to 76 ml/min per 100 g myocardium. The average change in the group amounted to $+31$ ml/min per 100 g ($P < 0.05$). One patient showed essentially no change in the myocardial clearance of rubidium after the administration of lignocaine, while in another patient the myocardial clearance fell. The statistical significance of the differences (P values) between the control values and the post-lignocaine values were calculated with the paired 't' test. This value was obtained by using the Hewlett-Packard 9810A calculator.

Lignocaine did not produce a significant change in the systemic blood pressure or cardiac rate.

Discussion

Donato *et al.* (1966) in their recent publication have stressed the safety and simplicity of the external counting method to measure coronary blood flow. Donato also states that this technique measures the average flow to the entire myocardial mass, independent of the venous drainage. Unperfused areas which do not contribute to the indirect Fick values, since they do not extract the indicator, contribute to the clearance values by the ^{86}Rb method in which the indicator content of the entire heart is averaged. Therefore, areas with no indicator actually contribute with their zero value to the average. Donato believes that the most significant advantage of this technique is that the flow value measured by the myocardial clearance of rubidium represents actual flow to true capillaries.

The main limitation to the method stems from dosimetric limitations. The small percentage of gamma radiations emitted by ^{86}Rb demands the use of relatively large radioactive doses, which limit the number of measurements that may be performed in the individual patient to a maximum of two. Further, the absolute flow cannot be determined with this method since individual variability in depth and size of the heart prevents an absolute estimate of myocardial uptake of the radioisotope. The obtained value for myocardial clearance represents the mean flow per unit mass, and it is conveniently expressed per 100 g myocardium.

In spite of these limitations, coronary blood flow measured by the ^{86}Rb method is reliable and reproducible. Donato measured coronary blood flow in the same patient with the N_2O saturation method as well as the ^{86}Rb external counting method. The average coronary blood flow values in the 11 subjects using the N_2O method was 72.0 ± 16.8 (SD) ml/min per 100 g myocardium, and in the same group using the ^{86}Rb method was 68.6 ± 16.1 (SD) ml/min per 100 g myocardium.

In a previous study in our laboratory (Gould *et al.*, 1972) we had determined that the average F value was 76 ± 13 per cent in 8 normal subjects studied with ^{86}Rb and 62 ± 22 per cent in 12 cases of stable coronary heart disease. The clearance of rubidium averaged 72 ± 21 ml/min per 100 g myocardium in the 8 normal subjects while in the 12 cases with coronary heart disease the mean value was 55 ± 20 ml/min per 100 g myocardium. These results were very similar to the values obtained by Donato and his associates.

In our present study, the average F value of 40 ± 19 as well as the clearance of ^{86}Rb of 45 ± 26 were lower than the values obtained previously in our stable coronary heart disease patients. This is not too surprising since the coronary blood flow

should be depressed in patients recovering from a recent myocardial infarction. After the administration of 100 mg of lignocaine, the average F value of 61 ± 10 and ^{86}Rb clearance value of 76 ± 32 were remarkably similar to our normal values. Thus, the depressed coronary blood flow in our myocardial infarction patients was returned to normal just by the administration of lignocaine.

However, one patient showed essentially no change in these variables after the administration of lignocaine while in another patient the myocardial clearance of rubidium actually fell. One can only speculate why these two patients differed in their response to lignocaine. It is of interest that the patient with the highest myocardial clearance of rubidium showed a decline in this value after lignocaine administration. Perhaps future studies will be required to ascertain if patients with a normal coronary blood flow after a myocardial infarction respond to lignocaine in a different manner from the patients with a depressed coronary blood flow.

Bloor and White (1969) had previously observed that small doses of lignocaine (0.25 mg/kg) produced an increase in coronary blood flow in 6 unanaesthetized dogs before and during coronary artery occlusion. When 2 mg/kg of lignocaine was administered, a decrease in coronary blood flow was seen. They concluded that lignocaine, at appropriate dosage, can promote collateral blood flow to the myocardium during coronary artery occlusion. An improvement in cardiac performance, after lignocaine administration, cannot explain the increased coronary blood flow.

The haemodynamic effects of an intravenous bolus of 100 mg lignocaine were recently studied in 8 patients with an acute myocardial infarction (Stannard *et al.*, 1968). The drug was shown to have no effect on the cardiac output, heart rate, systemic blood pressure, or pulmonary artery pressure. Grossman, Cooper, and Frieden (1969) also reported that the drug had negligible effects on left ventricular contractility.

The explanation for the rise in coronary blood flow that lignocaine produced in our myocardial infarction patients is of great theoretical and clinical interest. Oxygen consumption of the myocardium is a primary factor regulating coronary blood flow, and in general an increase in oxygen requirement increases the coronary blood flow. The various factors that affect myocardial oxygen consumption have recently been delineated (Sonnenblick, Ross, and Braunwald, 1968). Since lignocaine does not appreciably change the cardiac pressures, cardiac rate, or the velocity of contraction, a minimal alteration in the myocardial oxygen consumption cannot explain

the large increase in coronary blood flow observed in our patients. Thus, the coronary artery dilatation or an increase in collateral blood flow to the myocardium is the most likely explanation for the action of lignocaine.

The beneficial increase in coronary blood flow, produced by lignocaine, undoubtedly plays a major role in the antiarrhythmic action of the drug. The suppression of ventricular premature beats, in a patient with an acute myocardial infarction, would result not only from lignocaine's electrophysiological actions on the His Purkinje system but also from the increase in the blood flow to the myocardium. It is indeed possible that lignocaine may also limit the extent of the myocardial infarction by providing increased blood flow to marginally perfused areas. Perhaps a bolus of lignocaine should be administered to patients with a newly developed myocardial infarction not only to prevent arrhythmias but more importantly to increase the coronary blood flow. This possibility is certainly worthy of additional study.

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