APPLICATION OF THE HYDROGEN CATHETER ELECTRODE IN THE DETERMINATION OF CORONARY BLOOD FLOW

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Summary The H_2 catheter electrode was applied for the determination of the coronary blood flow to ascertain its applicability. First, a modified catheterization technique was newly introduced to facilitate the placing of the catheter tip in the coronary sinus. Secondly, using this technique, the catheter electrode was inserted into the coronary sinus of dogs. Then, the H_2 currents were measured in the aorta, coronary sinus and right atrium during the H_2 inhalation to obtain the blood flow rate per unit volume of the heart tissue. This flow measurement was performed under three different experimental conditions of hypoxic respiration, epinephrine infusion and intravenous injection of carbochromen.

In comparison of the present results with the previous data obtained by other authors, it was demonstrated that the H_2 current had sufficient accuracy and reproducibility to show the changes in coronary blood flow continuously over the long run of the experiment lasting for several hours. Unlike the results in the N_2O method based on the coronary sinus blood sampling, the H_2 desaturation curves recorded in the coronary sinus formed a straight line on the semilogarithmic scale. This suggested that the coronary blood flow observable in the coronary sinus might be almost uniform.

In the preceding paper (KOYAMA and MARUTANI, 1971) it was reported that the H_2 catheter electrode is useful for the determination of the coronary blood flow. The flow rate obtained by this method can be evaluated by measuring the P_{H_2} 's in both the coronary sinus and artery and it is generally expressed by a flow rate of ml blood per a unit volume of the heart per minute (ml/100 ml/min). Since the total individual heart volume can not be obtained, the absolute flow rate may not be obtained numerically. However, in the investigation of the effects of some chemical agents on the heart the use of this flow rate may be appropriate, since

Received for publication February 1, 1971

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individual variation of the heart size may be disregarded.

ECKENHOFF *et al.* (1947, 1948) found that the nitrous oxide saturation curve obtained in the coronary sinus was similar to that obtained in the atrium and concluded that the coronary sinus blood was contaminated with the atrial. To sample the coronary blood, therefore, their recommendation was to secure the catheter tip tightly inside the cardiac vein. When the P_{H_2} is measured directly at the catheter tip by using an H_2 electrode, however, the blood sampling is not necessary. Therefore, because the blood flow is present in the vicinity of the electrode surface, apprehension as to whether the P_{H_2} measured in the sinus would be affected by that of the atrium is unwarranted. Thus, it becomes desirable to leave a space between the catheter tip and the vascular inner wall to avoid disturbance of the blood flow, which might occur when the catheter tip is inserted deeply into the coronary vein as in the case of ECKENHOFF *et al.* (1947, 1948).

Hitherto, the coronary blood flow has usually been measured in open chest dogs, however, when it is technically possible to locate the catheter tip in the coronary sinus, the flow measurement should be made without opening the chest. Using this merit of the H_2 electrode, its applicability was examined in dogs without resorting to severe surgery. In addition, with the intention of demonstrating an expected increase of the coronary blood flow, measurements were made under the following three different conditions of hypoxic respiration, infusion of epinephrine and intravenous injection of carbochromen. The reliability of the method was further tested by comparing results obtained with the data presented by other authors.

METHODS

Three H_2 catheter electrodes were used for recording the P_{H_2} 's in the aorta, coronary sinus and right atrium. In some cases two electrodes placed in the aorta and coronary sinus were used. The introduction of the catheter was made principally according to Goodale's technique (GOODALE *et al.*, 1948), but it was found rather difficult to place the tip of the flexible conventional heart catheter in the desired position of the coronary sinus. To eliminate the technical difficulty a guide tube was improvised; this was a 30 cm long polyethylene tube with an outer diameter of 4 mm which was superimposed on the catheter at its distal end. The guide tube had a mild curvature of about 110 degrees at a point 1 to 2 cm from the tip. Since it had a suitable stiffness, the curvature was convenient for the introduction of the tip into the opening of the coronary sinus. As a preliminary step, the catheter was inserted through the tube so as to bring the electrode tip flush with the distal end of the tube, and the tube was fixed at its proximal end to the catheter by a rubber stopper which was previously set on the catheter. The inner lumen of the tube was filled with physiological saline solution by mild suction from the proximal end. With the aid of fluoroscopic observation the tip

of the tube could easily be introduced into the opening of the coronary sinus via the exposed jugular vein. After the introduction, the guide tube was bound to the jugular vein and by gentle prodding of the catheter the tip was moved into the coronary sinus and further into the coronary vein. Then, the tube alone was carefully pulled out, so that the distal end of the tube is removed from the atrium to the jugular vein, leaving the catheter electrode in the coronary vein. Finally, the catheter also was drawn outwards, so as to position its tip in the coronary sinus.

The recording of the H_2 current was made as described in the preceding paper (KOYAMA and MARUTANI, 1971) and the coronary blood flow was calculated from the recorded H_2 desaturation curve according to KETY and SCHMIDT (1945).

Mongrel dogs were anesthetized by intravenous injection of sodium pentobarbital in a dose of 30 mg/kg. Respiration was carried out through a tracheal cannula and a J-valve. In the hypoxia tests the hypoxic condition was maintained constantly for 10 min, then, a cock in the inspiratory system was turned to introduce the gas mixture containing hydrogen. In order to keep the alveolar P_{O_2} constant independent of the H_2 inhalation, O_2 concentrations in the inspired gases with or without H_2 were kept equal to each other.

In 6 to 8 min after the onset of the H_2 respiration the cock was returned to the previous H_2 free gas mixture to wash out the H_2 in the alveoli. The gas mixtures used had three levels of O_2 concentration of 5.38, 6.72 and 10.85% equally in both cases with or without H_2 . The H_2 concentration was usually lower than 5%. Each gas was prepared in high pressure bombs. In the control experiment of air respiration the dogs were subjected to an alternate respiration of room air and a gas mixture of 4.80% H_2 , 20.81% O_2 and a balance of N_2 .

Epinephrine was infused into the femoral vein in three different dose rates of 0, 0.5, and 1.0 $\mu\text{g/kg/min}$. Carbochromen (Takeda, Osaka) which is known as a coronary vasodilating substance was injected intravenously in a dose of 2 mg/kg and the coronary blood flow was measured at 15 and 45 min after the injection.

RESULTS

Figure 1 shows the P_{H_2} changes in the aorta, coronary sinus and right atrium in four different experimental conditions of air respiration, epinephrine infusion, carbochromen injection and hypoxia. The P_{H_2} changes were most rapid in the aorta, slower in the coronary sinus and the slowest in the atrium. The rate of the change depended on the flow rate, in detail, the time to reach the saturation points or the maximum plateaus varied according to the flow rate within a range of 2 to 7 min. Figure 1 A shows the P_{H_2} curves obtained in air respiration. Figure 1 B was obtained under intravenous infusion of epinephrine, where the P_{H_2} change in the sinus became very rapid. Under the influence of carbochromen the curve was found to be less steep than in epinephrine infusion as shown in Fig. 1 C,

Fig. 1. Recordings of hydrogen concentration in the aorta, coronary sinus and right atrium of a single dog. A, Control; B, epinephrine infusion at a rate of $1.0 \mu\text{g/kg-min}$; C, intravenous injection of carbochromen in a dose of 2 mg/kg ; D, respiration of 5.38% oxygen.

but clearly steeper than in the control of air respiration. In the hypoxic respiration the H_2 curve of the coronary sinus became remarkably steep.

Figure 2 shows the desaturation or washout curves obtained in three different cases of hypoxia, epinephrine and carbochromen administrations from top to bottom, where the P_{H_2} was expressed in percentage of the maximum plateau value. All the curves were obtained one after another in the same dog employed for obtaining the data of Fig. 1. Figure 2A shows the curves measured in three different P_{O_2} levels of 20.81, 10.85 and 5.38% O_2 gas inhalations. The calculated coronary blood flows were 99, 165 and 426 ml/100 ml/min in the above cases, respectively. Figure 2B shows the H_2 curves during epinephrine infusion under three different dose rates of 0, 0.5 and 1.0 $\mu\text{g/kg/min}$. When 0.5 $\mu\text{g/kg/min}$ was given, the blood flow increased from 99 up to 160 ml/100 ml/min and when the dose rate was doubled, the flow rate increased further to 325 ml/100 ml/min. Figure 2C shows the desaturation processes measured 15 and 45 minutes after the intravenous injection of carbochromen in a dose of 2 mg/kg, where the calculated flow rates were 232 and 147 ml/100 ml/min, respectively. In the recording of Fig. 1 all the saturation processes proceeded more slowly than the desaturation for unknown reasons. Even when the blood flow, however, was calculated from the saturation curves the obtained values showed no systematic difference from those obtained using desaturation process.

Figure 3 shows the relationship between the coronary blood flow and O_2 concentration in inspired gases obtained in 15 dogs. The coronary blood flow at O_2 concentrations of 20.92, 10.85, 6.72 and 5.38% were found to be 93.6, 128.5, 310.2 and 454.5 ml/100 ml/min on average, respectively. The standard deviations were 24.3 ($n = 23$), 25.7 ($n = 11$), 62.0 ($n = 12$) and 92.3 ($n = 4$), respectively, where n denotes the number of experiments. The above average flow rates in hypoxia correspond to 146.8, 331.5 and 485.0% of the rate of the control, showing a wide variability of the coronary blood flow. In parallel with the coronary blood flow, the aortic blood pressure and the heart rate also increased as the P_{O_2} was decreased. The mean aortic pressures together with the standard deviations in four cases of the above were 121.9 ± 14.7 , 135.0 ± 15.0 , 142.6 ± 10.0 and 184.0 ± 10.2 mmHg and the heart rates were 165.2 ± 26.0 , 164.0 ± 29.0 , 204.8 ± 15.0 and 212.6 ± 11.6 beats/min. During severe hypoxia the R-spike of ECG was lowered in most cases, and arrhythmia appeared at times.

Figure 4 shows the effect of carbochromen of the coronary blood flow in relation to the elapsed time after the injection of carbochromen. In six dogs carbochromen was intravenously injected in a dose of 2 mg/kg. In all dogs the coronary blood flow increased clearly. On an average the control value was 79.8 ± 15.3 ml/100 ml/min, while 15 and 45 min after the injection the calculated flow rates were 132.5 ± 54.0 ml/100 ml/min ($P < 0.05$) and 99.8 ± 28.5 ml/100 ml/min ($P < 0.10$), respectively. These flow rates corresponded to 166.0 ± 67.5 and $124.7 \pm 35.6\%$ of the control value. The mean aortic pressure

Fig. 2. Tracings of the desaturation curves in the same dog as in Fig. 1 under various conditions of hypoxic respiration, epinephrine infusion and treatment with carbochromen.

Fig. 3. The relation between the coronary blood flow observed and the oxygen concentration of the inspired gases. The thin horizontal lines indicate the average values.

Fig. 4. Coronary blood flow obtained 15 and 45 minutes after intravenous injection of carbochromen in six dogs.

Fig. 5. Corondry blood flow observed under intravenous infusion of epinephrine in four dogs.

and the heart rate showed no definite changes.

In four dogs the effects of epinephrine infusion were investigated at dose rates of 0.5 and 1.0 $\mu\text{g/kg/min}$. The drug did not always increase the coronary blood flow but a considerable variation was observed in measured flow rates as shown in Fig. 5. The flow rates ranged from 132 to 330% of the respective control values. The responses in the heart rate as well as in the mean aortic pressure also differed from case to case. In one dog which showed only a slight increase in coronary blood flow both the heart rate and mean aortic pressure showed a slight decrease by epinephrine infusion. In another dog which showed considerable increase in coronary blood flow the heart rate decreased at a dose rate of 1.0 $\mu\text{g/kg/min}$, while the mean aortic pressure increased steadily. In other words, no consistent tendencies were observed in either the heart rate or the mean aortic pressure. Thus, it may be said that the dogs employed showed a considerable individual variation in response to epinephrine infusion.

In Fig. 6 the three H_2 curves in the coronary sinus shown in Fig. 1 were re-plotted at every 40 sec on a semilogarithmic scale against the elapsed time. All curves showed a linear decrease, indicating a homogeneous blood flow through the coronary vessels in spite of the regional variation in dimension of individual vascular routes.

The curves obtained in the atrium may reflect the blood flow through the

Fig. 6. Semilogarithmic plotting of the hydrogen desaturation curves of Fig. 1.

entire body, where individual vascular routes should be different from part to part of the body. Thus, it was expected that the H_2 curve in the atrium would deviate from such a simple exponential curve as shown in Fig. 6. Consequently, it seemed rather difficult to obtain an average blood flow through the entire body from the H_2 curve. As an example to show the specific characteristic of this H_2 curves, logarithms of the P_{H_2} 's in the atrium and the coronary sinus were plotted against time in both the cases of control and epinephrine infusion in Fig. 7. The atrial H_2 curve was found to be multiexponential and was tentatively resolved into two components as shown with the broken lines in Fig. 7. For each component the blood flow could be calculated by replotting each of the broken lines on a linear scale and by applying the method by Kety and Schmidt. In the control experiment the fast component yielded a flow rate of 59.0 ml/100 ml/min and the slow component showed a flow rate of 17.0 ml/100 ml/min. Epinephrine infusion made the slope of the fast component steeper and that of the slow, less steeper than that of the respective component in the control, *i. e.* the flow rates were 117.5 and 14.7 ml/100 ml/min.

DISCUSSION

As for the effect of continuous hypoxic conditions ECKENHOFF *et al.* (1948) found that the coronary blood flow was increased from 66.0 to 150 ml/100 ml/min in dogs in 8% O_2 inhalation, and HACKEL *et al.* (1954) reported that the coro-

Fig. 7. An example of component analysis of H_2 desaturation curves replotted from Fig. 1A and B. The atrial curve was tentatively divided into two linear broken lines.

nary blood flow increased from 116.8 to 193.3 in 10% O₂ inhalation and from 126.3 to 502.5 ml/100 ml/min in 5% O₂ inhalation, which coincided with the present results.

According to NITZ and PÖTZSCH (1963) the coronary blood flow increased by 66% of the control value at 15 min after an injection of 2 mg/kg of carbochromen and 25% at 45 min. RUDOLPH *et al.* (1967) found an increase of 45% at 15 min. In the present study the increase of coronary blood flow was 66.0 and 24.7% at 15 and 45 min, respectively, which were in good agreement with the previous data described above.

The effect of epinephrine on the coronary blood flow have hitherto been studied by observing the influence of a single injection thereof. PITT *et al.* (1967) found a 194% increase following a single intravenous injection of 1.0 µg/kg of epinephrine using an implanted magnetic flowmeter. Because of the difference in procedure of giving epinephrine, their results can not be compared directly with ours. In our experiments the coronary blood flow clearly increased in three dogs out of four with the administration of epinephrine. Therefore, at least in that a strong increase of the coronary flow was found, our data agreed with theirs.

ECKENHOFF *et al.* (1948) found that the N₂O desaturation curve in the coronary sinus was similar to that in the atrium. On the other hand, KIRK and HONIG (1964) reported a nonuniform distribution of capillary vessels through the myocardium. However, as shown in Fig. 6 the H₂ desaturation curves in the coronary sinus apparently showed a straight line on a semilogarithmic scale under three different conditions. This seems to suggest that the coronary blood flow was almost uniform through the entire region of the heart muscle. Recently, we found in another experiment that the coronary flow was different in quantity more or less in various layers of the myocardium. Therefore, it may be conceivable that the regional variation of the coronary flow is not so large as to be detectable by the H₂ desaturation curve obtained in the coronary sinus.

As reported in the preceding paper KOYAMA and MARUTANI (1971) a linear relation between the H₂ current and P_{H₂} can only be obtained in a narrow range of the measuring conditions. However, such conditions were not so difficult to obtain, *i.e.* when optimum conditions for thickness of the platinum black layer, tightness of the covering Teflon membrane, and so on were attained, the linear calibration curve could be obtained. On the other hand, in order to know the P_{H₂} from the H₂ current it was necessary to maintain the P_{O₂} in the measuring site constant. In the measurement of the coronary blood flow, it is necessary in general to keep the P_{O₂} in the myocardium as constant as possible. Therefore, the P_{O₂}'s of the inspired gases with and without H₂ were carefully adjusted to a constant level. Then, the influences of some extrinsic agents exerted on the coronary vessels may be appreciated with accuracy.

Another undesirable drawback of the present method for the flow measurement seems to lie in length of time required to know the flow rate which exceeds

10 minutes. This drawback is essentially concerned with diffusibility and solubility of H_2 in the muscle as well as the volume ratio of the flowing blood and the muscle tissue of the heart. For instance, if the H_2 molecules were as less diffusible as dyes generally used in a dye dilution method, the blood flow velocity may be obtained in a very short time. However, in such a case the flow rate per a unit volume of the heart could never be obtained. Therefore, it should be recognized that in order to appreciate the blood volume flowing through the unit volume of the organ tissue a length of time such as 10 to 15 min becomes absolutely necessary. Thus, the technical drawback of requiring a considerable length of time, rather than being the end result of using the H_2 electrode, may be the intrinsic limitation of this type of measurement.

The authors wish to express their thanks to Prof. M. Mochizuki, Director of the Research Institute of Applied Electrocitry, Hokkaido University for his valuable suggestions in the present study.

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