CATHETER SEMICONDUCTOR RADIATION DETECTOR FOR CONTINUOUS MEASUREMENT OF CARDIAC OUTPUT

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The use of radioisotopes for biological studies often requires *in vivo* detection of beta activity. A detector that can be inserted into living subjects will make it possible to get new information which is unobtainable by conventional external measurement of radioactivity. The detector for this purpose must be small, harmless to living tissue and adequately sensitive.

Previously, a catheter micro G-M counter was used for this purpose with a certain degree of success (*1–3*). In our laboratory, this microminiaturized G-M counter was inserted into the canine heart and coronary circulation time was measured (*4*). However, the application of this counter to clinical diagnosis was limited because of such drawbacks as rapid deterioration due to radiation, high operating voltage and restricted sensitivity to high-energy beta rays such as are emitted by ^{32}P.

Recent developments on a semiconductor detector overcame these disadvantages and are opening new possibilities in this field. Taking notice of important characteristics of this detector, such as smallness, durability and low operating voltage, the authors made a p-n junction detector into a catheter detector and investigated its use in the field of clinical medicine.

The first part of this paper describes the construction of a catheter semiconductor detector probe, an outline of the electronic system and some properties of the catheter semiconductor detector system. The results regarding continuous measurement of cardiac output are presented in the second part of this paper. Other clinical applications are also discussed.

CONSTRUCTION AND CHARACTERISTICS OF CATHETER SEMICONDUCTOR DETECTOR

Design and construction of the catheter semiconductor detector and its associated circuits. A catheter semiconductor radiation detector probe (CASRAD probe, supplied now by Tokyo Shibaura Electric Co., Ltd. as "Catelix") was designed for *in vivo* measurement of beta activity in blood or tissue. The electron spectra from beta decay consist of continuous distribution, and the energy of the electrons decreases as they pass through blood or tissue. Consequently, the beta-ray spectrometer is not necessary in *in vivo* measurement, and the beta-ray counter is sufficient.

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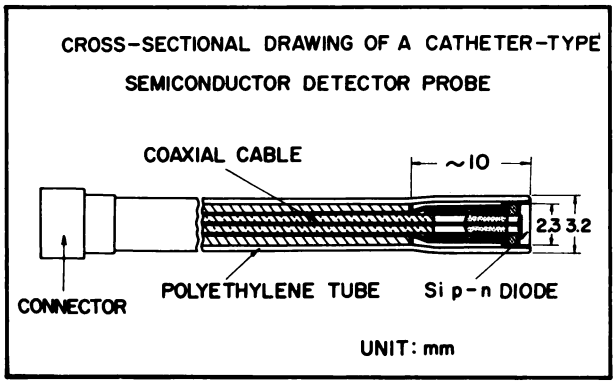

FIG. 1. A cross-sectional drawing of standard disk-type catheter semiconductor radiation detector (CASRAD) probe.

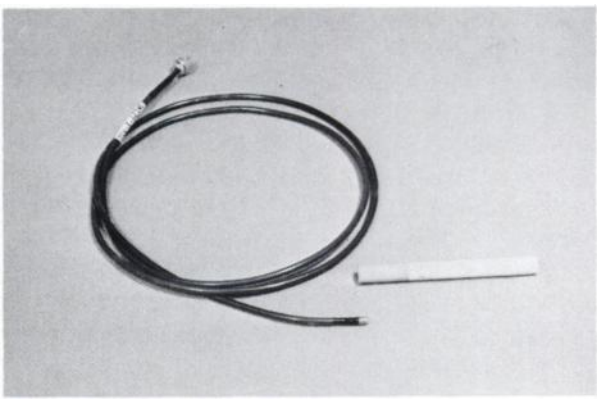

FIG. 2. Photograph of CASRAD probe. Outer diameter of probe is about 3.2 mm.

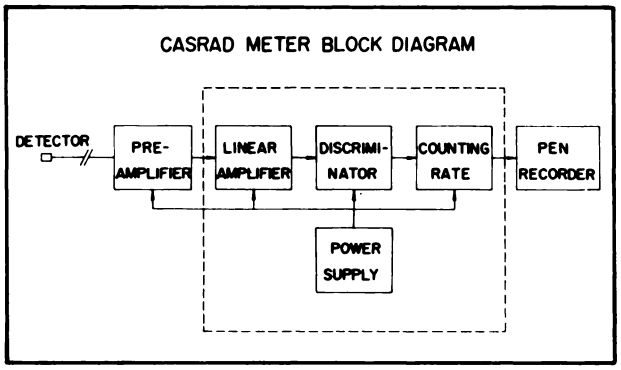

FIG. 3. Block diagram of CASRAD electronic system.

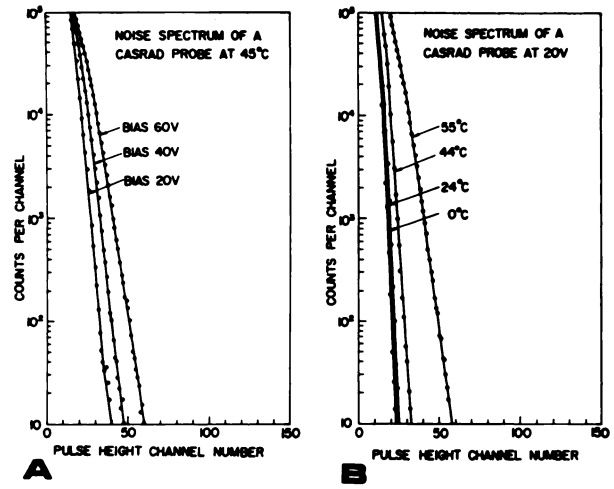

FIG. 4. A is noise spectrum of CASRAD probe at temperature of 45°C. B is noise spectrum of CASRAD probe at operation voltage of 20 volts.

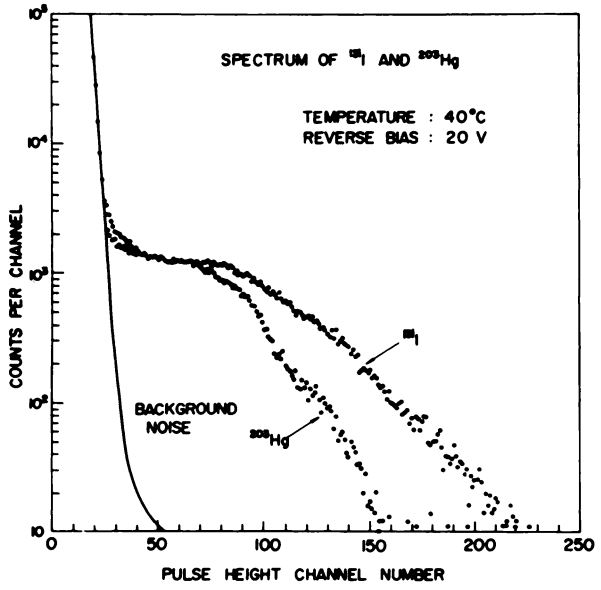

FIG. 5. Spectrum of ^{131}I and ^{203}Hg measured by CASRAD probe.

Thus a silicon p-n junction detector was chosen as the detector element of the probe instead of a lithium-drifted silicon detector.

Figure 1 shows a cross-sectional drawing of a disk-type CASRAD probe that was used in the experiments on animals. A silicon p-n junction diode, 2.3 mm in dia and 1 mm thick was used as the detector element. The diodes were made from vacuum-float-zoned boron-doped p-type silicon ingots with a resistivity ranging from 3,000 to 5,000 ohm-cm and with a minority carrier lifetime greater than 500 μsec. To prevent the deterioration of the p-n junction edge, the diode was protected with a silicon dioxide film, approximately 3,000 Å thick, which was deposited on the surface of the diode by a fast pyrolytic deposition method (*5*). This diode was connected to one end of a specially developed subminiature noiseless coaxial cable approximately 120 cm long. The entire probe was then covered with a polyethylene tube to make it watertight. The maximum outer diameter of this CASRAD probe is about 3.2 mm. Figure 2 is a photograph of a CASRAD probe.

The signals from a CASRAD probe are small because there is no internal amplification in the silicon p-n junction detector and the total capacitance of the probe is relatively large. Therefore, the amplifier system must have a much higher gain and a much lower noise level than the amplifier for a micro G-M counter.

Figure 3 shows a block diagram of the CASRAD electronic system. The components of the circuitry used in this system are a preamplifier, linear amplifier, discriminator, counting ratemeter and a pen recorder. All components except the pen recorder were completely transistorized to eliminate microphonic noise and to reduce the circuit voltage to ensure further safety.

Some properties of the catheter semiconductor detector system. Figure 4 A and B shows the noise spectrum of a CASRAD probe. As shown in Fig. 4 A, the noise level is seen to increase in proportion to the increase of the reverse bias. In Fig. 4B the noise level increases with the rise of temperature although the rate of increase is small. It was concluded that the noise could be easily discriminated by setting the discriminator properly, e.g. setting at 60 channels was sufficient for $\lesssim$ 40°C and $\lesssim$ 40-volt bias.

When an ordinary subminiature coaxial cable was used, burst noises, which have a much higher pulse height compared to radiation signal, were induced whenever the cable was bent. Therefore, a special subminiature noiseless coaxial cable was developed for the probe.

The spectrum of ^{131}I and that of ^{203}Hg are shown in Fig. 5. In these measurements a CASRAD probe of 20-volt bias was immersed in solutions of ^{131}I and ^{203}Hg at a temperature of 40°C. The maximum energy of beta rays from ^{131}I is 815 keV and that from ^{203}Hg is 214 keV. Therefore this probe can be used to detect beta-ray sources with a maximum energy greater than 200 keV which exist in the body fluid.

Figure 6 shows the beta-ray detection efficiency of a CASRAD probe as a function of reverse bias voltage. In this measurement, the probe was immersed in a ^{32}P solution. The counting rate increased with the increment of reverse bias up to about 10 volts, but it became nearly independent of the reverse bias beyond this voltage.

Figure 7 shows the relative counting rate as a function of the ^{32}P concentration in the solution. The linearity was proved to be satisfactory.

The isoresponse curve of the detector is shown in Fig. 8. In this measurement, ^{32}P was used as a point source of radiation. At a distance of 0.5 cm in air, the response decreased to 5% of the surface value and to 0.1% at a distance of 5 cm. This result indicates the capability of significant spatial resolution.

Discussion. The development of a CASRAD probe with a smaller diameter was essential for intracardiac introduction into the human body. Recently a probe of about 2.7 mm o.d. was developed in our laboratory and is now being used extensively. The basic construction of this probe is the same as the disk-type probe shown in Fig. 1.

A further modified CASRAD probe with a single-ended coaxial element has also been developed to improve the detection efficiency and spatial response of the disk-type probe. The detection efficiency of the coaxial probe developed so far is several times as large as that of the disk-type probe with the same diameter. The details of the probes mentioned above are to be published in the near future.

The fact that the CASRAD probe is safe electrically has also been clarified. The signal line of the probe to which the bias voltage is applied is completely insulated from the living subject as is shown in Fig. 1. Even in the event of insulation failure, only a negligible current would flow into

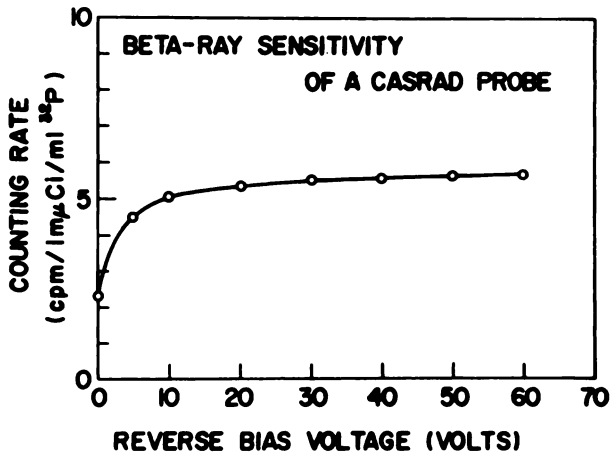

FIG. 6. Detection efficiency for beta rays of CASRAD probe as function of reverse bias voltage; ^{32}P is used as source.

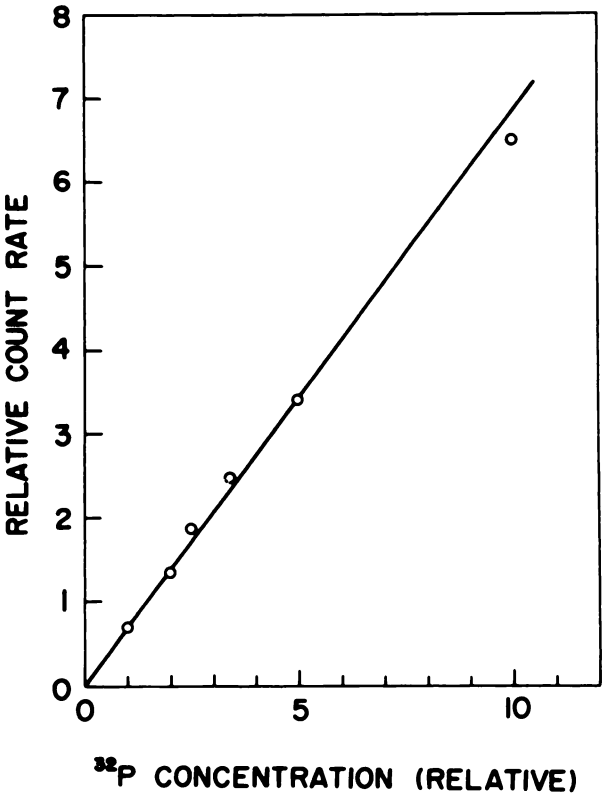

FIG. 7. Lineality between radioisotope concentration and counting rate.

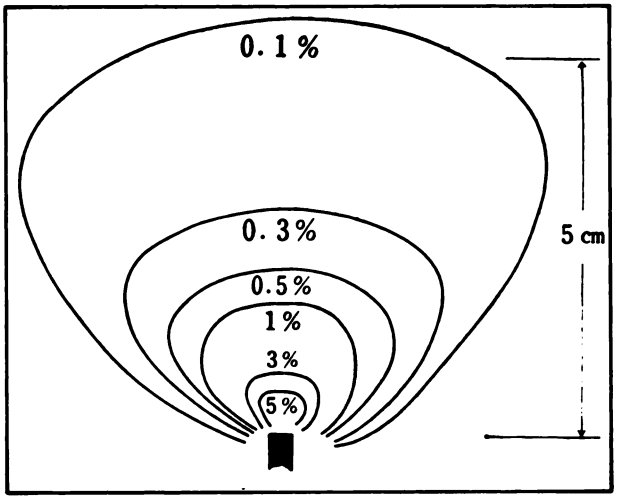

FIG. 8. Isoresponse curve to ^{32}P in air.

the body. This current is calculated to be as small as 1 μA and is believed to be quite safe. According to Starmer *et al* (*6*) the current of 180 μA causes ventricular fibrillation, but a current below 10 μA which is about 20-fold lower than the lowest fibrillation current is considered to be safe.

This leakage current is calculated as follows: The voltage applied to the signal line is fed through a series resistor which is located in the preamplifier placed outside the body. The current flowing through the body is calculated by the following equation, provided the resistivity of the reverse-biased detector is far greater than that of the body.

$$i = V/(R + Rh) \qquad (1)$$

in which

i = current through the body
V = applied bias voltage
R = resistivity of the series resistor
Rh = resistivity of the living subject.

The resistivity of the series resistor was chosen to be about 20 MΩ, and the resistivity of the living subject is estimated at some thousands of ohms. Then supposing the value of V to be 20 volts, a leakage current of about 1 μA is obtained from Eq. 1.

Due consideration must also be given to another electric hazard: As is shown in Fig. 1, the shield of the probe is also completely insulated from the living subject and is grounded. Even in the event of insulation failure, no current would ever flow into the body provided other electronic instruments are not used at the same time. However, if instruments without grounding were to be used, the current might flow from the ground lead of the probe into those of the other instruments and then a fatal electric shock might occur. To safeguard against this hazard, the ground lead of the probe together with those of other instruments should always be kept at ground potential.

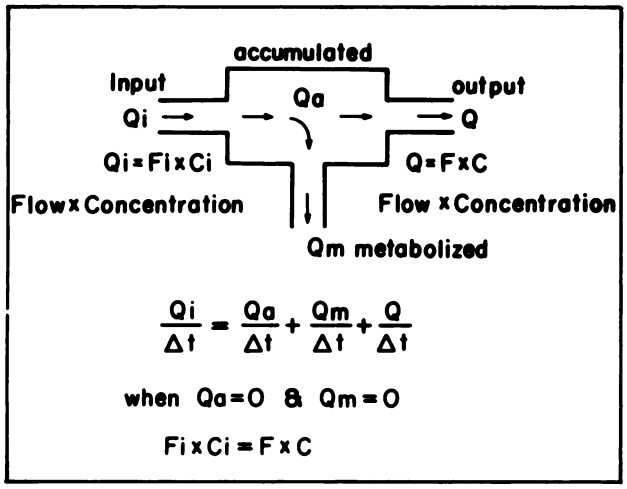

FIG. 9. Principle of measurement of regional blood flow using CASRAD probe. Recirculation is not taken into consideration.

CONTINUOUS MEASUREMENT OF CARDIAC OUTPUT

When a certain quantity of indicator is infused, it flows into the region and, after it becomes mixed and diluted completely, it escapes from the region. If one chooses a substance which neither accumulates nor metabolizes in the region, the simple formula in Fig. 9 can be obtained according to the principle of conservation of material.

When ^{85}Kr is intravenously injected (a 99% beta emitter), more than 95% is exhaled into expiratory air during the first pulmonary circulation under normal ventilation, resulting in negligible recirculation (*7*). Therefore, the equation in Fig. 9 can also be applied in the case of a living body where recirculation exists. The equation becomes

$$F = (Fi \times Ci)/C. \qquad (2)$$

In this report, ^{85}Kr saline solution was intravenously infused at a constant speed (Fi). According to Eq. 2, the change in the right cardiac output (F) is measured by continuous monitoring the concentration (C) in the right ventricle. Also by measuring the initial concentration of ^{85}Kr (Ci) using the same probe, the absolute value of the right cardiac output can be calculated.

METHODS AND MATERIALS

Flow-model study. The validity of the principle expressed in Eq. 2 was investigated using a flow model. A constant-flow system was set up using a water tank and a polyvinyl tube (about 1 cm in dia.). The flow rate, which could be changed by altering the diameter of the input tube, was determined by directly collecting the outflow water into a graduated cylinder. The ^{85}Kr solution was infused continuously at a constant rate, using a Harvard pump, into the upper stream of the system. The rate of ^{85}Kr dilution in the stream was continuously detected by the CASRAD probe. The change in the counting rate measured by the CASRAD probe was compared with the actual flow rate changes.

Canine experiments. The following experiments were performed using 21 mongrel dogs, weighing 4.5–17 kg under nembutal anesthesia (0.25 mg/kg).

1. The ^{85}Kr saline solution (3–5 mCi/ml) was infused into the femoral vein at a constant speed using a Harvard pump. After ^{85}Kr became completely mixed with the total systemic venous return,

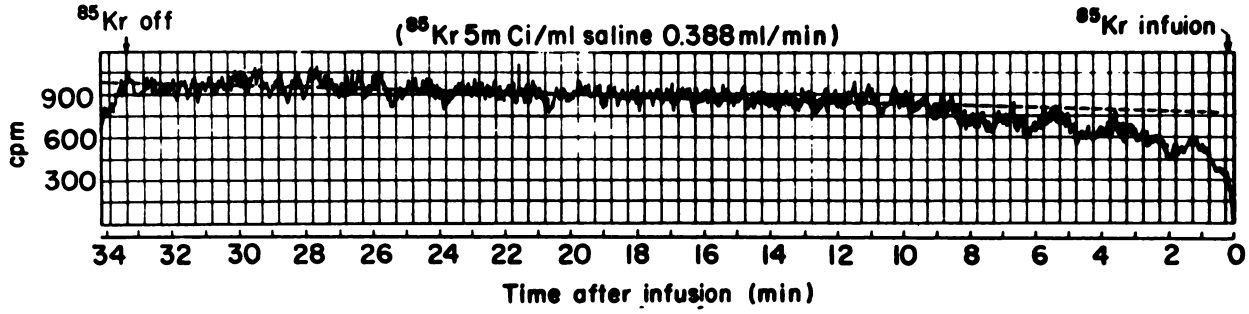

FIG. 10. Continuous measurement of cardiac output in nembutal anesthetized dog.

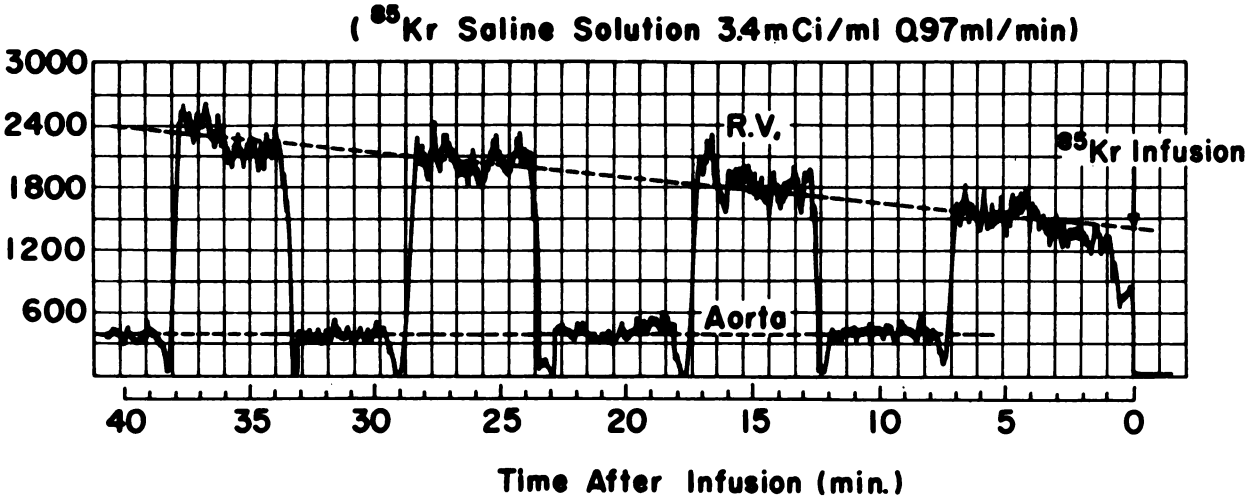

FIG. 11. Measurement of right cardiac output and recirculation of ^{85}Kr measured in aorta. Counting rate in right ventricle increases gradually, whereas counting rate in aorta remains constant, indicating gradual decrease of cardiac output in nembutal anesthetized dog.

radioactivity was measured by the CASRAD probe inserted through the jugular vein into the outflow tract of the right ventricle. To investigate the rate of recirculation of ^{85}Kr, the second probe was placed in the descending aorta through the carotid artery. The positions of the probes were confirmed by x-ray fluoroscopy.

2. Changes in cardiac output were induced in dogs by the intravenous injection of epinephrine, and its effects on cardiac output were observed by this method.

3. The validity of this method was evaluated by comparing the values of cardiac output obtained by this method and those by the IHSA dilution method. Immediately after measuring the right cardiac output by the CASRAD method, 20–40 μCi of IHSA was injected intravenously and arterial blood samples were drawn serially from the femoral artery. The radioactivity of ^{131}I in the blood samples was measured by a well scintillation counter. The cardiac output was calculated according to the Stewart-Hamilton method using the ^{131}I-IHSA dilution curve.

4. The mean value of the left cardiac output was measured by an electromagnetic flowmeter attached at its head to the root of the aorta. At the same time, the radioactivity of the ^{85}Kr solution infused through the left atrium was detected by a CASRAD probe placed in the root of the aorta. The changes in cardiac output observed by these two methods were compared.

RESULTS

Flow-model study. The results of the two experiments are presented in Table 1. The water flow was changed five times in each of the two experiments in the range of 21.5–106.0 ml/sec and 14.6–55.6 ml/sec. The product of counting rate detected by a CASRAD probe and actual flow rate ($F \times C$) was found to be constant in each experiment. The mean values of $F \times C$ in the two experiments were 637.3 ± 9.3 (1 s.d.) and 370.9 ± 20.7 (1 s.d.), respectively, and deviations from mean values ranged from −3.6 to +4.4% (mean 0 ± 2.8%) and from −9.8 to +6.2% (mean 0.4 ± 5.5%), respectively.

TABLE 1. CONTINUOUS FLOW MEASUREMENT USING FLOW MODEL

	Counts (cps)	Flow (ml/sec)	C × F	Deviation %
A 1	13.7	27.8	370.2	+0.8
2	5.4	71.0	383.4	+4.4
3	3.5	106.0	371.0	+1.0
4	3.9	85.0	357.0	−2.8
5	16.5	21.5	354.8	−3.4
		mean	367.3 ± 9.3	0 ± 2.8
B 1	11.4	34.0	380.5	+2.6
2	27.0	14.6	394.0	+6.2
3	20.7	17.6	364.3	−1.8
4	11.4	33.5	381.9	+3.0
5	6.0	55.6	333.6	−9.8
		mean	370.9 ± 20.7	+0.4 ± 5.5

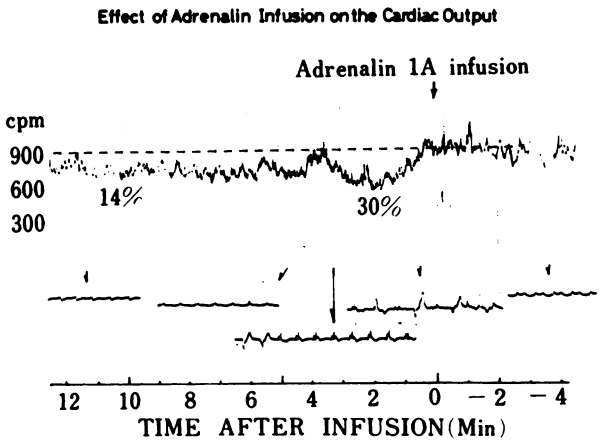

FIG. 12. Effect of epinephrine on cardiac output. Decrease of counting rate after epinephrine injection means increase of cardiac output.

Canine experiments. The results of the continuous measurement of cardiac output in an anesthetized dog are shown in Fig. 10. The counting rate vs. time was observed to increase linearly at the rate of 1%/min. Although the counting rate in the right ventricle increased continuously, the counting rate of the recirculated ^{85}Kr measured by the detector in the aorta remained constant (Fig. 11). Accordingly, the gradual increase of the counting rate in the right ventricle indicated the gradual decrease in cardiac output in the dog.

The change in cardiac output induced by epinephrine was recorded by this method. The effect of epinephrine on cardiac output was not always the same, but varied, case by case. Cardiac output increased in some cases but decreased in others. An example shown in Fig. 12 revealed a 30% increase in cardiac output immediately after an injection of 1,000 μg of epinephrine, followed by an increase of 14% for more than 10 min.

The results of five comparison studies of cardiac output in regard to the CASRAD technique and IHSA dilution method are presented in Table 2. The differences in cardiac output obtained by the CASRAD technique and by the IHSA dilution method were +47.2%, +6.1%, −10.4%, −17.0% and −32.6%; 1 s.d. of the differences equalled 27.2% and the correlation coefficient was 0.72.

The gradual decrease of cardiac output in nembutal-anesthetized dogs was also observed during the intercalibration between the CASRAD method and the electromagnetic flow meter. The ratio of decrease at 10, 15 and 20 minutes was 10.0%, 25.0% and 30.5%, respectively, by the CASRAD method, and 11.6%, 20.7% and 25.6%, respectively, by the electromagnetic flowmeter (Table 3).

Discussion. Cardiac output has hitherto been measured conventionally by indirect methods such as Fick's method and dye- or radioisotope-dilution methods. These methods are clinically useful but not suited to serial or continuous determination of cardiac output. Recently, much attention has been directed to the application of direct methods using thermal, differential pressure, ultrasonic and electromagnetic flowmeters. By these means changes in the blood flow can be continuously measured. Among them the electromagnetic flowmeter is currently most widely used, and because it can record rapid flow changes, even pulsatile flow changes can be detected. The one drawback is that operative procedures are necessary because the probe must be attached to exposed vessels. On this account, improvement and introduction of nonoperative techniques were developed to record the regional blood flow in the intact body continuously. For this purpose, catheter-type flowmeters such as thermal and differential pressure flowmeters were developed and have succeeded to a certain extent. The thermal flowmeter is more suitable for measuring venous flow than arterial flow (*8*). Since the differential pressure method as well as the use of electromagnetic and ultrasonic flowmeters measure the change in velocity, it is necessary to know the vessel diameter in converting the obtained value into volume flow based on the flow-velocity relationship (*9*). The demand for a simple and reliable clinical flow-measuring device is yet to be satisfied, and the determination of cardiac output still remains a challenging problem, even though various methods are currently in use.

The CASRAD method introduced in this report is a new approach to continuous cardiac output measurement based on a technique using infusion of ^{85}Kr as an indicator. The major difference between

this method and the conventional indicator dilution technique requiring either blood sampling or external measurement is that regional radioactivity can be continuously detected with a miniaturized probe inserted into the vessels.

Experiments using the flow model revealed that the counting rate was inversely proportional to the flow rate. This result was considered to be proof of the validity and reproducibility of this method as a continuous measurement of flow changes. Changes in cardiac output induced by epinephrine injections were successfully measured by this method in anesthetized dogs.

As shown in this study, the recirculation of ^{85}Kr becomes negligible following its injection into the circulation because it is almost completely expired from the lung. Therefore this isotope is extremely suitable to be used as an indicator in the measurement of cardiac output. Because of the short biological half-life of this nuclide, the patient's exposure to radiation is very small with the doses used—0.5 rad/hr to the lung and 1.6 mrad/hr to the whole body. Therefore, the continuous measurement of cardiac output can be safely performed for long periods.

A comparison between the cardiac-output values determined by the CASRAD method and those by the IHSA dilution method revealed a fairly satisfactory agreement. A comparison of the CASRAD method with the electromagnetic flowmeter method in recording the changes in cardiac output also showed good agreement.

Rochester *et al* (*10*) and Cornell *et al* (*11*) measured cardiac output by the blood sampling method using ^{85}Kr as an indicator. In view of the insolubility of ^{85}Kr in blood and saline solution (solubility coefficient to water is 0.05), considerable care must be taken to avoid the entrance of even the smallest of air bubbles into the injectate. This problem offers a difficulty in the accurate calculation of the amount of indicator used. Care should also be taken in handling the sampling blood not to lose any of the rare gas. Even though blood sampling is not necessary, our method also requires the counting rate of the injectate to be measured accurately to determine the absolute value of cardiac output.

Another major concern in this study is the completeness of ventricular mixing of the indicator injected. The site of injection and sampling of the indicator is an important factor of the mixing. Maseri *et al* (*12*) compared the values of cardiac output obtained by dye-dilution curves sampled at various sites with those obtained by IHSA radiocardiogram. Even though ventricular injection with ventricular outflow sampling yielded false low value

TABLE 2. COMPARISON OF CARDIAC OUTPUT MEASURED BY CASRAD METHOD AND IHSA DILUTION METHOD

		Cardiac output % difference		
Dog	Weight (kg)	IHSA method l/min	CASRAD method l/min	From IHSA method
1	7.7	1.63	2.44	+47.2
2	9.5	1.79	1.53	−17.0
3	9.5	2.22	2.01	−10.4
4	9.5	1.51	1.67	+ 6.1
5	10.0	0.89	0.60	−32.6
			mean −1.3 ± 27.2	
			r = 0.73	

TABLE 3. COMPARISON OF CARDIAC OUTPUT MEASURED BY CASRAD METHOD AND ELECTROMAGNETIC FLOW METER

	CASRAD method		Electromagnetic flow meter	
Time (min)	Counting rate (cps)	Decrease (%)	Flow rate (ml/min)	Decrease (%)
10	16.2		913.5	
15	18.0	10.0	797.5	11.6
20	21.6	25.0	725.0	20.7
25	23.3	30.5	681.5	25.6
			r = 0.94	

of the cardiac output, atrial injection with ventricular outflow sampling as well as atrial or ventricular injection with pulmonary artery sampling gave cardiac output values in good agreement with those of the reference method. In our study the detections were made in the outflow tract of the right ventricle following the continuous infusion of the indicator into the femoral vein. In such an instance, fairly satisfactory mixing is expected according to the previous report.

Although it is still technically difficult to insert the detector into the pulmonary artery, further improvement of the detection place is now being performed by the development of a smaller CASRAD probe which is suitable for insertion into both human and canine pulmonary arteries. Also in our findings the absence of dips and staircase changes in time-concentration curves indicated the presence of homogeneous mixing.

The cardiac cyclic movement is also a factor of mixing. Irisawa *et al* (*13*) reported that the saline concentrations of the two points in the ventricle after the 4th cardiac beats following single injection of saline solution were in fairly good agreement (86.5%) in the 215 records. In our study, however, the cyclic change of concentrations, if present,

does not cause any error in the measurement since the recording is smoothed out by the setting of a large time constant.

The main advantage of the method is its capability of observing the right cardiac output continuously, without operative procedure, by simply using the right-heart catheterization technique. The application of the method to clinical cases is now in progress with the development of a smaller disk-type or single-ended coaxial-type detector, the diameter of which is further reduced to about 2.7 mm. This size is small enough to be inserted into the human peripheral veins.

The CASRAD is applicable for various purposes in clinical medicine other than continuous flow measurement (*14–16*). Among them, measurement of circulation time, cardiac-shunt detection and diagnosis of malignant tumor in the upper gastrointestinal tract have been studied.

An example of measurement of circulation time from the femoral vein to the inferior vena cava is shown in Fig. 13. The radioactivity of ^{85}Kr was detected by the CASRAD probe which was inserted into the inferior vena cava. The appearance time was 2.5 sec and the peak time was 9.0 sec in this case. To investigate the applicability of the detector to shunt detection, left-to-right shunt was artificially produced between the carotid artery and the jugular vein in a dog. ^{85}Kr was injected into the left ventricle and was detected in the right ventricle by the CASRAD probe. When the shunt was open, as shown in Fig. 14, an early significant peak of radioactivity was observed. This peak disappeared when the shunt was closed.

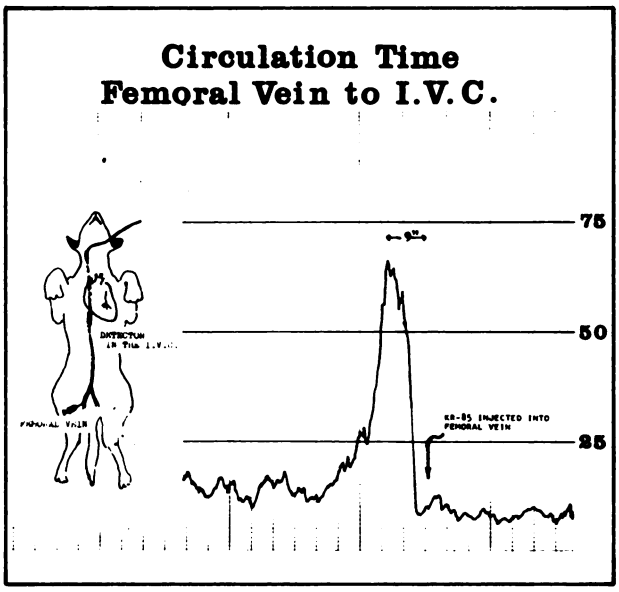

FIG. 13. Measurement of circulation time from femoral vein to inferior vena cava.

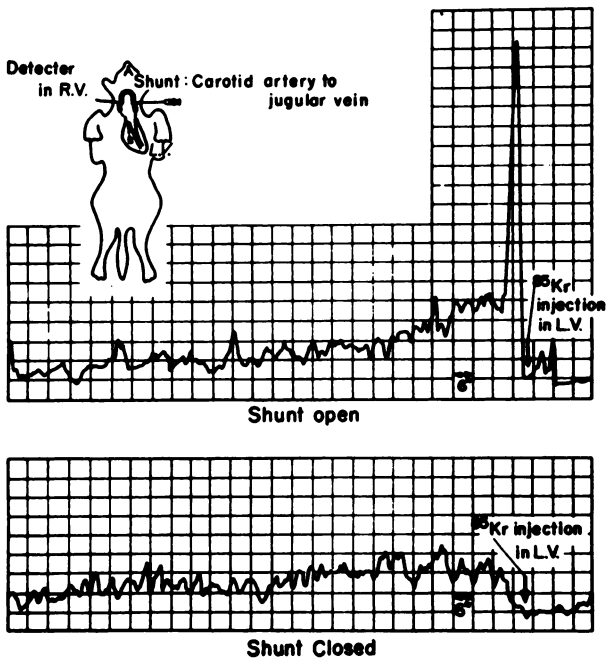

FIG. 14. Detection of left-to-right shunt.

SUMMARY

The catheter semiconductor radiations detector (CASRAD) was developed for *in vivo* measurements of beta radiation in blood and tissue. The detector element is a silicon p-n junction diode which is 2.3 mm in dia and 1 mm thick. The specially developed subminiature noiseless coaxial cable, approximately 120 cm long, is connected to the detector head. The entire probe is covered with a polyethylene tube to make it watertight. The maximum outer diameter of the probe is about 3.2 mm, and a completely transistorized low-noise charge sensitive preamplifier was developed to eliminate microphonic noise.

The following are some of the important characteristics of the detector: A low operating voltage of 10–40 volts with constant sensitivity in this range; lineality between counting rate and radioisotope concentration; sufficient noise discrimination and good spatial resolution. It was proved that this detector can be safely inserted into the body and is suitable for measuring localized beta activity *in vivo*.

The CASRAD probe was used to continuously measure the right cardiac output based on flow-dilution relationship with ^{85}Kr saline solution used as an indicator. In the studies performed on anesthetized dogs, the probe was placed in the outflow tract of the right ventricle where it detected the ^{85}Kr radioactivity infused at a constant rate into the

femoral vein. Changes in the cardiac output caused by epinephrine injections were recorded continuously by this method. Comparison of the CASRAD method with IHSA dilution and electromagnetic flowmeter methods in the determination of cardiac output revealed good agreement between the results.

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