PRELIMINARY NOTES

A Precision Flow-Controlled Rb-82 Generator for Bolus or Constant-Infusion Studies of the Heart and Brain

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A precision flow-controlled rubidium-82 generator has been constructed to deliver 76-sec Rb-82 at either fast or slow flow rates for bolus or constant-infusion studies. A stepping motor drive is interfaced to a microprocessor for pulsed control of flow rate to deliver the saline eluant solution from a large-volume (150 ml) machined pumping syringe through an alumina column that retains the 25-day Sr-82 parent. The generator system delivers 70–90% of the maximum Rb-82 activity in a 20–25 ml bolus elution of 2% NaCl. The Sr-82/Sr-85 breakthrough is 10^{-7}–10^{-6}. Both yield and breakthrough are functions of column length and flow rate. Six separate Sr-82 loadings of the generator were evaluated over a period of nearly 2 yr in studies of myocardial blood perfusion and permeability changes in the blood-brain barrier. Sterility and apyrogenicity of the Rb-82 eluate were maintained during multiple elutions and long-term use of 3–4 mo for each generator loading.

J Nucl Med 22: 1006–1010, 1981

The potential of positron emission tomography for quantitative studies of flow and metabolism by noninvasive methods has created a need for readily obtainable short-lived positron emitters. Generator-produced radionuclides partly answer this need. In addition there is a requirement for the positron emitters to have a half-life appropriate to the physiological problem being explored and commensurate with good statistics at low radiation exposure to the patient.

The 76-sec positron-emitting Rb-82 daughter of 25-day Sr-82 meets these requirements, though the half-life is somewhat shorter than ideal for flow studies. As much as 60 mCi of Rb-82 is obtained in a 20–25 sec bolus elution from an alumina-column generator that retains the Sr-82. Repeat elutions can be done every 5–10 min, at which time the background activity in the subject has decayed away and the generator has recharged close to its maximum radioactive level.

Development of the Rb-82 generator over the past 12 yr has led to the present precision flow-controlled system (*1–5*). Other investigators have also pursued the development of Rb-82 generators in the last 6 yr (*6,7*).

Precisely controlled infusion requirements have led to the development of a unique flow-rate controller and pumping system with a large-volume (150 ml) reservoir. It delivers a sterile solution of Rb-82 in 2% NaCl from an alumina-column Sr-82 generator at either slow or fast elution rates and operating pressures of 50–100 psi.

Generator-produced Rb-82 is infused intravenously as a bolus or at constant or variable elution rates to obtain quantitative studies of the heart, head, or kidneys with positron-imaging instruments.

MATERIALS AND METHODS

Figure 1 is a schematic of the Rb-82 generator, which has an open-loop stepping-motor drive* with a wide dynamic speed range and adequate torque, particularly at low speeds. A timing belt connects the stepping motor

Received April 3, 1981; revision accepted June 30, 1981.

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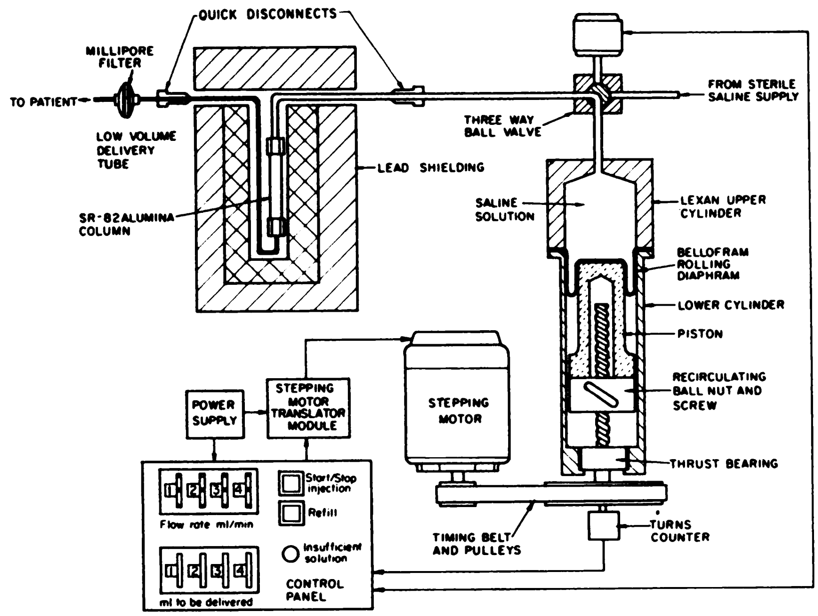

FIG. 1. Schematic of Rb-82 generator, with stepping-motor drive, microprocessor control, large-volume pumping syringe, motorized valve control, control panel, quick disconnects, and double lead shielding for the alumina column charged with Sr-82.

to a recirculating-ball nut and screw that moves the stainless steel piston inside a machined Lexan barrel. A rolling diaphragm[†] around the piston provides the pumping unit with a low-friction seal against airborne bacteria. The entire pumping system is mounted on FR-4 glass-epoxy for electrical isolation of the patient.

Quick disconnects permit the pumping unit—consisting of the Lexan barrel, piston, Bellofram diaphragm (neoprene or silicone rubber), stainless steel lines, and column—to be autoclaved before the generator is assembled and loaded with Sr-82. Subsequent loadings of Sr-82 require autoclaving only the column components and not the pumping system.

The motor controller is a microprocessor[‡] with 4K memory, a crystal clock, a programmable timing module, two RS-232 serial ports, and an 8-bit analog-to-digital converter. Additional input-output functions are provided by 3-state buffers and addressable latches. The function of the controller is to convert input from the operator into a precise number of timed pulses for the stepping motor. The microprocessor minimizes operator error by simplifying the controls and doing the calculations, counting, and timing.

The front panel of the controller has two four-digit thumbwheel switches and two lighted pushbutton switches. The thumbwheels determine flow rate (ml/min) and volume to be delivered (ml). One pushbutton switch initiates the pump-refill operation. The other starts the injection, or stops an injection in progress. After power-up or reset, the microprocessor initializes itself and sets up the timing module and serial ports. It then jumps into a looping program that scans the two pushbutton switches and the thumbwheel switch specifying volume. It thus monitors changes in switch settings, scanning at greater than 1000 times per second. When a change is detected, the new setting is stored and the program enters a service routine for that particular switch. The first part of each routine is a delay that guarantees that the new setting is stable for at least 50 msec. The delay eliminates problems caused by contact bounce.

Another part of the loop program ascertains how much solution is left in the pump. A voltage picked off a ten-turn potentiometer, which is coupled to the piston-drive screw with a timing belt, is fed to the analog-to-digital converter and is compared with the previously stored reading from the thumbwheel switch. If the operator has asked for more solution than is in the pump, the program sets up a circuit in the programmable timing module that causes the INSUFFICIENT lamp to flash twice a second. An injection cannot be started in this state; the operator must either refill the pump from the solution reservoir or change the amount to be delivered.

The outlet from the pump is connected to a motor-driven three-way valve[‖] by ⅛-in. s.s. tubing and Swagelok fittings. The three-way valve allows connection to either the saline fill bottle when the controller is in the REFILL position or to the Sr-82/Rb-82 alumina column when the controller is in the ELUTION position.

The filling sequence is started when the loop program has determined that the FILL pushbutton has been actuated. The fill service routine turns on the REFILL pushbutton light to inform the operator that filling has started. The routine next turns on the valve motor, waits for the correct valve position, then sends 100-sec pulses to the stepping motor in the reverse direction until the pump reservoir is filled; it then turns on the valve motor again, waits for correct position, turns off the REFILL light, and reenters the loop program.

The last part of the loop program determines whether the START/STOP pushbutton has been activated. If it has, the program sends a start command through the serial port to the host computer used with the positron ring tomograph. The host computer acknowledges the command, and starts taking data. The patient cannot be injected inadvertently, since the pump will not start unless the acknowledge is received. While this handshaking process is going on, the service routine reads the flow-rate thumbwheel switch and computes the period T during which pulses are to be sent to the stepping motor, where

$$T\ (\text{msec}) = \frac{6 \times 10^4}{FC};$$

here F is the flow rate in ml/min and C is a systems constant. For this pumping system, the systems constant is 257 pulses to the stepping motor to deliver 1 ml of solution.

The quantity of injected solution is determined by counting the number N of pulses sent to the stepping motor, where

$$N = QC$$

where Q is the number of milliliters to be delivered, as indicated by the thumbwheel switch.

The system described thus far will do constant-infusion or bolus-infusion studies. Variable-infusion studies can be done by calculating constants, using programs residing in the host computer, and then sending these constants to the microprocessor controller through the serial port.

Other schemes to control the quantity of solution injected were considered. An integrating dosimeter using a flowthrough plastic-scintillator positron detector could be used to monitor the activity injected into the patient, but this would involve undesirable complexity and cost. Furthermore, the dose of Rb-82 is predictable within ± 5% from the decay-corrected Sr-82 on the column and the volume and flow rate of the elution.

Figure 1 also shows the inner and outer lead shielding for the Sr-82/Rb-82 source. The outer lead shield (7.6 cm thick) is bolted to the generator system. The inner shield (5.1 cm thick) houses the stainless steel column (6.9 mm i.d. × 95 mm) filled with 100–200-mesh basic alumina. The inner lead shield and alumina column are removed from the main shielding and pumping system for loading with up to 200 mCi Sr-82 and potentially 600 mCi of contaminating Sr-85 that is produced by the spallation reaction of high-energy protons on the molybdenum target at Los Alamos (*8*). The Sr-82 loading is done by remote handling in a "hot cell" with an auxiliary automated pumping system.

After the loading of the column, elutions from the Rb-82 generator are done with 2% NaCl (pH 8–9) until the breakthrough of Sr-82/Sr-85 is less than 1 ppm; the column is then relocated in the main shielding at the site of the positron ring tomograph. The breakthrough, sterility, and apyrogenicity of the eluate are determined for each new column loading, and periodically throughout the 3–4 mo useful life of the Rb-82 generator. The breakthrough of Sr-82/Sr-85 is maintained at less than 0.01 μCi per elution. If the breakthrough exceeds this value, a small alumina trapping column is placed in the outflow line.

Stainless steel lines, 1/8 in. o.d., 1/16 in. i.d., are used to connect the column to the pumping system and serve as the outflow line to the sterile membrane filter and three-way valve. From this valve a PE 200 polyethylene tubing, 0.035 in. i.d., is used for the direct intravenous infusion of the elution bolus for studies of myocardial perfusion, blood-brain barrier abnormalities, and intravascular brain blood flow. For continuous-infusion studies PE 50 polyethylene tubing, 0.023 in. i.d., is used to connect directly to the intravenous catheter. Because of the slower flow rate required during continuous infusion studies, narrower tubing is used to reduce the Rb-82 decay loss in transit to the patient.

Bolus elution yields of Rb-82 were determined at a flow rate of one ml/sec for 3–30 sec. The elapsed elution time was determined by the fractional elution volume and by the Sr-82 activity on the column. For either the fractional or total elution yield, the elution volume was collected, assayed in an ionization-chamber dose calibrator, and decay corrected to the time at the end of elution. After waiting 30 min for the Rb-82 to decay away, the collected elution volume was counted in a well counter and the breakthrough of Sr-82/Sr-85 was calculated for a 20-ml elution volume; the reference standard was Sr-82/Sr-85, as previoiusly described (*2*).

Constant-infusion yields of Rb-82 and the steady-state radioactivity levels were determined for flow rates from 2.2 to 5.3 ml/min. The radioactivity was collected at a constant flow rate and measured in the dose calibrator every 30–60 sec from 0 to 20 min. The breakthrough was calculated by the same method used for the bolus elution.

The effect of column length on breakthrough and Rb-82 yield was determined for 9.5- and 10.0-cm-long columns under bolus-elution conditions.

RESULTS AND DISCUSSION

The present version of the Rb-82 generator has been in continuous use for the last 2 yr. In this time the Sr-82/Sr-85 breakthrough, Rb-82 elution yields, column design, and effects of long-term use with large elution volumes have been studied.

Figure 2(a) shows the fractional elution of Rb-82 per 3-ml fraction collected at a flow rate of 1 ml/sec for 27 sec. The peak of the Rb-82 activity is obtained in the fractions collected from 6–15 ml (aggregate volume 9 ml). In actual bolus-infusion studies, the elution volume delivered to the patient is calculated to administer the permissible radiation dose, which is 60 mCi for Rb-82. Normally, 20 mCi is the dose of Rb-82 used for each study.

Figure 2(b) reflects the cumulative Rb-82 yield when the total dose of 27 ml bolus infusion is administered to the patient. In this case 95% of the Sr-82 activity on the column is eluted as Rb-82.

After initial washings following the loading of Sr-82/Sr-85 on an alumina column, the breakthrough is maintained at 10^{-7}–10^{-6} for rapid bolus elutions. At the slower elution rates required for constant infusion studies, the breakthrough decreases by an order of magnitude.

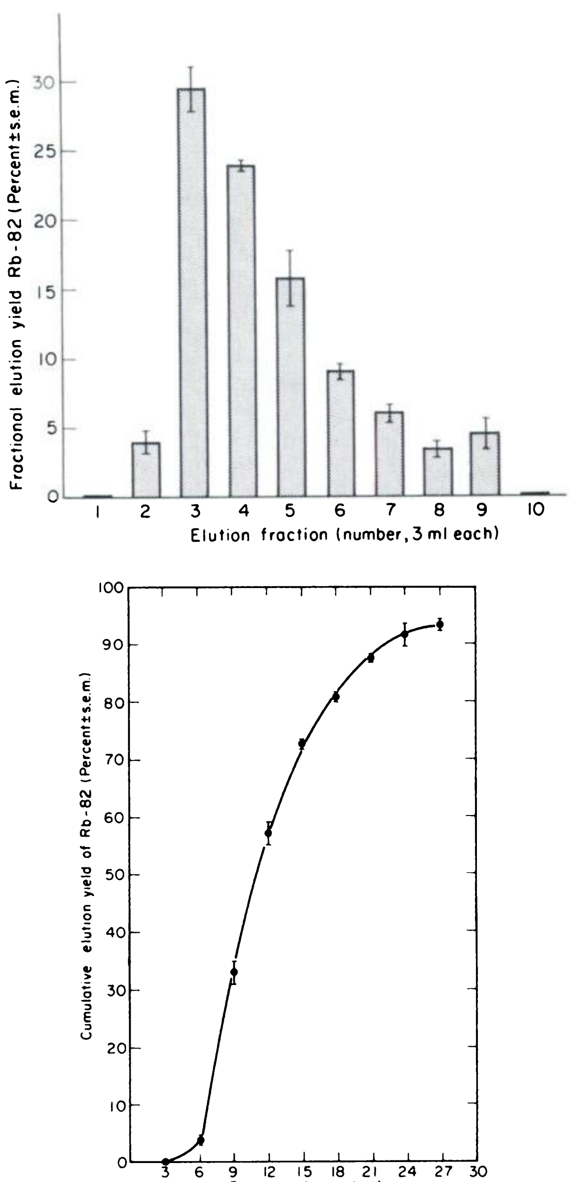

FIG. 2. (a) Fractional elution yield of Rb-82 from Sr-82 on alumina column 6.9-mm i.d. × 95 mm. Flow rate was 1 ml/sec of 2% saline; nine 3-ml fractions were collected over 27 sec. Each point is mean of three determinations. (b) Cumulative yield of Rb-82 under same conditions as in Fig. 2(a). Yield of Rb-82 is 95% when decay corrected to time at end of elution.

The length of the alumina column affects both the Rb-82 yield and the Sr-82/Sr-85 breakthrough. In Figure 2(b) a 9.5-cm-long column was used to give a 95% yield of Rb-82 for a 27-ml bolus elution. A 10.0-cm-long column gave an 85% yield for a 33-ml bolus elution. The breakthrough of Sr-82/Sr-85 ranged from 10^{-6} to 10^{-7} for the 9.5-cm column and from 10^{-7} to 10^{-8} for the 10.0-cm columns. A compromise between Rb-82 yield and Sr-82/Sr-85 breakthrough, at least for bolus elutions, determines the specification of the alumina column.

There is some overlap in the breakthrough relative to a 5% difference in column length. Other unmeasurable factors such as pre-washing the alumina and the technique of packing the alumina column can affect the breakthrough from identical columns loaded with Sr-82. However, the breakthrough is predictable within an order of magnitude, which is adequate for the low breakthrough from the alumina column, normally ranging 0.01–0.001 μCi.

Constant infusion requires a slower infusion rate to achieve a steady state or equilibrium condition, which is a function of input, extraction rate, tissue washout, and radioactive decay. Dynamic positron tomographs can collect the information in short time frames of several seconds to provide information on the input, the steady-state condition, and the washout. Tomographs that require a few minutes for sampling can use the constant-infusion method for equilibrium imaging or static imaging during biological decay from the equilibrium condition.

The relationship between flow rate and radioactivity under steady state is shown in Fig. 3, which indicates that the radioactivity level for Rb-82 is determined by the flow rate through the generator column. At the faster flow rate of 5.3 ml/min, about 20 mCi of Rb-82 is delivered to the subject at the steady state, which is attained

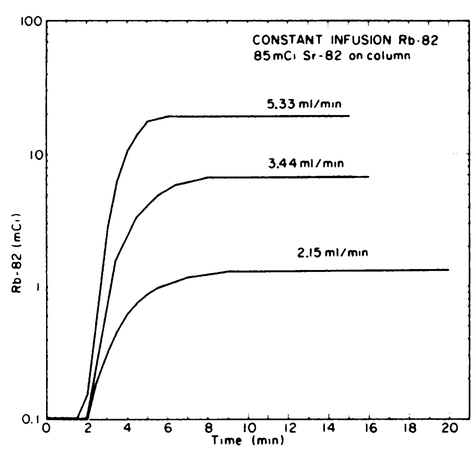

FIG. 3. Yield of Rb-82 at constant infusion rates as a function of flow rate, which determines Rb-82 activity at steady state.

in 6 min after the start of elution from 85 mCi of Sr-82 on the alumina column. The total dose delivered to the patient is a function of the length of time the infusion remains under steady state, plus the amount accounted for in the initial washin phase and the final decay phase after the infusion is stopped. At the slower flow rate of 2.2 ml/min, about 1.2 mCi of Rb-82 is delivered at the steady state, which is attained in about 9 min.

Previously a new alumina column was prepared for each loading with Sr-82. However, we now find it possible to recharge the same alumina column with Sr-82 at least three times without significant increase in Sr-82/Sr-85 breakthrough. Use of the same column again minimizes the radiation dose and greatly reduces the time and effort required for charging the generator with a new batch of Sr-82.

The Sr-82 generator is a reliable source of a useful positron emitter for the study of heart, brain, or kidneys with positron tomography.

We report elsewhere (*9–11*) the use of rubidium-82 in human subjects as an indicator of myocardial perfusion or changes in the blood-brain barrier.

ACKNOWLEDGMENTS

The authors thank Barbara Alford for technical assistance and Drs. H. A. O'Brien and P. M. Grant of Los Alamos Scientific Laboratories for providing the spallation-produced strontium-82 used in this work.

We also thank Mary Graham and Linda Lutgens for preparation of this manuscript.

This work was supported by the U.S. Department of Energy under Contract No. WW-7405-ENG-48.

This work was presented in part at the 27th Annual Meeting of the Society of Nuclear Medicine, Detroit, Michigan, 24–27 June 1980.

FOOTNOTES

* Slo-Syn Stepping Motor, manufactured by the Superior Electric Company.

† Bellofram Diaphragm, manufactured by the Bellofram Corporation.

‡ Motorola M6800.

‖ Hoke three-way ball valves, 316 s.s., ⅛-in. Gyrolok connections, Hoke, Inc., Cresshill, NJ.

REFERENCES

1. YANO Y, CAHOON J, BUDINGER TF: Precision flow-controlled Rb-82 generator for bolus and constant infusion. *J Nucl Med* 21:P85, 1980 (abst)
2. YANO Y, BUDINGER TF, CHIANG G, et al: Evaluation and application of alumina-based Rb-82 generators charged with high levels of Sr-82/85. *J Nucl Med* 20:961–966, 1979
3. YANO Y, ROTH EP: An alumina column Rb-82 generator. *Int J Appl Radiat Isot* 30:382–385, 1979
4. YANO Y, CHU P, BUDINGER TF, et al: Rubidium-82 generators for imaging studies. *J Nucl Med* 18:46–50, 1977
5. YANO Y, ANGER HO: Visualization of heart and kidneys in animals with ultrashort-lived ^{82}Rb and the positron scintillation camera. *J Nucl Med* 9:412–415, 1968
6. GRANT PM, WHIPPLE RE, O'BRIEN HA JR, et al: The influence of carrier strontium level and eluant volume on the performance of (Sr-82)-(Rb-82) biomedical generators. *J Nucl Med* 19:1250–1255, 1978
7. GRANT PM, ERDAL BR, O'BRIEN HA JR: A Sr-82–Rb-82 isotope generator for use in nuclear medicine. *J Nucl Med* 16:300–304, 1975
8. GRANT PM, O'BRIEN HA JR, KAHN M: The isolation of Sr-82 from 200 to 600 MeV proton irradiated Mo targets for biomedical applications. *J Inorg Nucl Chem* 37:413–417, 1975
9. BUDINGER TF, DERENZO SE, HUESMAN RH, et al: Dynamic emission transaxial tomography for positron emitters. In *Frontiers in Nuclear Medicine.* Horst W, Wagner HN, Jr, Buchanan JW, Eds. Berlin, Springer-Verlag, 1980, pp 52–70
10. BUDINGER TF, YANO Y, DERENZO SE, et al: Myocardial uptake of rubidium-82 using positron emission tomography. *J Nucl Med* 20:603, 1979 (abst)
11. BUDINGER TF, YEN C-K, YANO Y, et al: Blood brain barrier permeability and intravascular flow-volume measurements using rubidium-82 and dynamic positron emission tomography. *J Nucl Med* 22: P15, 1981 (abst)
12. YEN C-K, BUDINGER TF: Evaluation of blood brain barrier permeability changes in Rhesus monkeys and man using Rb-82 and positron emission tomography. *J Comput Assist Tomogr*, in press.