A REMOTE SYSTEM FOR THE ROUTINE PRODUCTION OF OXYGEN-15 RADIOPHARMACEUTICALS

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ABSTRACT

The details of the construction and operation of a remote, automated system for the production of oxygen-15 labeled radiopharmaceuticals are described. This system routinely provides oxygen-15 labeled oxygen, carbon monoxide, and water directly to the PET imaging facility, in quantities and purities suitable for human studies.

Keywords: radiopharmaceutical, oxygen-15, positron emission tomography

INTRODUCTION

Oxygen-15 labeled radiopharmaceuticals (^{15}O-O_2, ^{15}O-CO, ^{15}O-H_2O) have become increasingly important for studies of oxygen metabolism, blood volume, and blood flow, respectively, using positron emission tomography (PET)(1-3). The short half-life of oxygen-15 (2.04 min) allows for rapid sequential studies using any combination of these three radiopharmaceuticals: for example, in studies of regional blood flow changes during visual stimulation, eight injections of ^{15}O-H_2O (each 50-100 mCi) can be made in less than 2 hours total time (4).

We and others have previously reported the production of these oxygen-15 radiopharmaceuticals in quantities and radiochemical purities suitable for human studies (5-11). In our institution, these radiopharmaceuticals are used multiple times each day. The reliable and routine production of these radiopharmaceuticals (over 1900 preparations in 1984) has required construction of a remote, automated apparatus for production and delivery. We describe here the details of our present system.

0362-4803/85/111193-08$01.00

Received May 24, 1985
Revised June 24, 1985

EXPERIMENTAL

The oxygen-15 production system can be broken down into three sections: (1) the cyclotron target, (2) the gas transport lines and furnaces for chemical conversions, and (3) the automated bubbling system for the production of ^{15}O-H_2O.

Cyclotron target. The cyclotron target is essentially the same as was installed on the beam line in 1972 (12). The target is constructed of aluminum with a volume of 132 cc, covered in front by a double foil assembly using 0.25 mil Havar foils. Irradiations are performed using the Washington University School of Medicine Allis-Chalmers cyclotron (6.2 MeV deuterons) at a beam current of 40 microamps.

O-15 Gas Handling System. The system for the production of the three gases ^{15}O-O_2, ^{15}O-CO, and ^{15}O-CO_2, is a slight modification of,

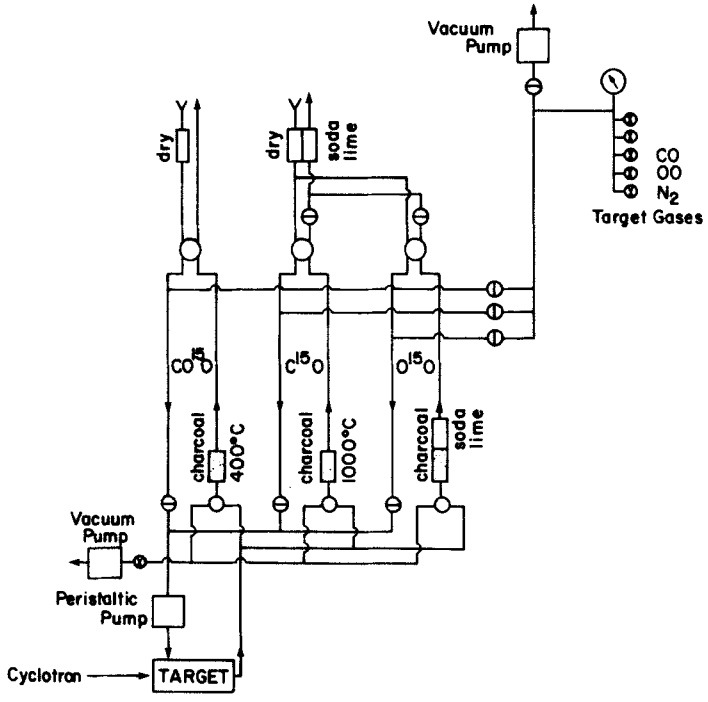

Figure 1. Schematic of gas transfer system for the remote production of oxygen-15 labeled gases.

and an improvement on, a system which has been in operation for 12 years. The system is shown schematically in Figure 1. There are three separate but interconnected gas transfer loops, constructed using 3/16 inch OD nickel tubing and air driven ball valves (Whitey Model 131SR). The charcoal furnaces are constructed using ceramic tubes (14 in. long, 1 in. dia., McDanel Refractory Porcelain Co, PA) and heated with Lindberg furnaces. The carbon dioxide traps (12 in. long, 0.5 in. dia.) on the ^{15}O-O_2 and ^{15}O-CO lines are filled with 4-8 mesh soda lime (Fisher Scientific) The total volume of each loop is approximately 350 cc (including target).

For ^{15}O-CO_2 and ^{15}O-O_2 production, the target and loop are filled with 2% oxygen in nitrogen (15 psi). For production of ^{15}O-CO, the target and appropriate loop are filled with nitrogen (15 psi). During irradiation, the target gas is circulated at the flow rate of 3 L/min using a large peristaltic pump. At the point where sufficient oxygen-15 has been produced (usually 3 microamp-hour), the ^{15}O-O_2 and ^{15}O-CO are sent directly to the PET imaging facility via line L1, using a bolus of high pressure nitrogen. There the gas is collected in a sterile breathing bag located in a shielded cart, monitored by a CsF detector. As an alternative, the radioactive gases can be collected in a sterile breathing bag located inside a wide-bore ionization chamber. For ^{15}O-H_2O production the ^{15}O-CO_2 is routed to the bubbling apparatus, as described below.

Oxygen-15 water production. The ^{15}O-H_2O is produced by the exchange of ^{15}O-CO_2 with water, as previously described (6). The apparatus used is shown in Figure 2. The ^{15}O-CO_2 produced in the gas loop and target is bubbled through a specially designed bag (Medex Inc, Hilliard, Ohio) held in a 2 inch dia. ionization chamber (the readout from this ionization chamber is displyed at the cyclotron control desk). The bag is filled with 8-10 ml of sterile saline prior to cyclotron target bombardment. Bubbling is accomplished using the peristaltic pump: after passing through the bubbling bag and through a drying tower (Ca_2SO_4), the gas is recirculated back into the target for

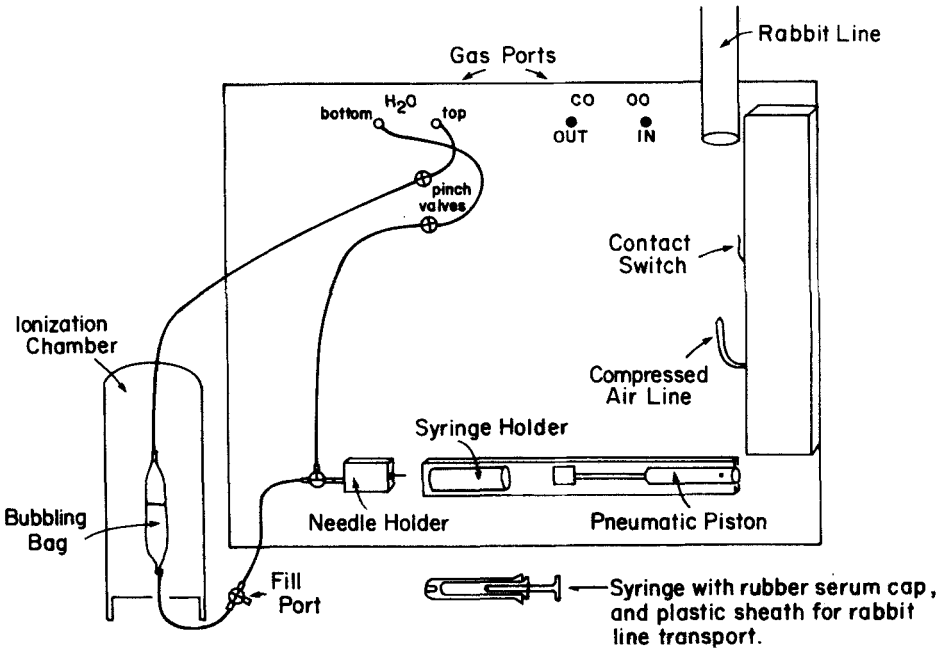

Figure 2. Remote apparatus for production of O-15 labeled water via exchange between O-15 carbon dioxide and water.

further irradiation.

When sufficient ^{15}O-H_2O has been produced (usually 150 mCi), the bubbling is stopped, and the contents of the bag drawn into a sterile 12 ml syringe usinge the pneumatic piston. The syringe is capped with a rubber septum. When full, the syringe is automatically injected (using a short blast of compressed air) into the pneumatic transfer system, and sent to the PET imaging facility. The syringe is delivered directly into an ionization chamber.

Quality control. Strict quality control procedures have been instituted with this system. Radionuclidic and radiochemical purities are determined by gas chromatography (GC) using a Varian 3700 chromatograph fitted with a gas sampling valve,a CTR I column (Alltech Assoc.), and gas proportional counter (13). TheCTR I column used has concentric columns, with an inner column of 6' x 1/8 in. Porapak and an

Table 1. Radionuclidic and radiochemical purities of oxygen-15 labeled gases produced in remote system. Analysis by gas chromatography (CTR I column, helium carrier gas: see Experimantal). Values shown were determined at EOB + 2 minutes.

impurities	$^{15}O_2$	$C^{15}O$	$C^{15}O_2$
^{13}NN	1-2%	1-2%	1-2%
^{15}OO	---	0-.5	0-.5
$C^{15}O$	0-.5	---	1-2
$C^{15}OO$	0-.5	0-.5	---

outer column of 6' x 1/4 in. activated molecular sieve. This column is capable of separating N_2, O_2, CO, and CO_2. For ^{15}O-O_2 and ^{15}O-CO, the radionuclidic (^{13}N-N_2) and radiochemical (^{15}O-CO_2) impurities must be kept to a minimum. For ^{15}O-CO_2, the radionuclidic and possible radiochemical impurities (^{15}O-CO, ^{15}O-O_2) are of no consequence, as they are not trapped in the saline during the bubbling procedure used to produce ^{15}O-H_2O.

The typical radionuclidic and radiochemical impurities observed in the O-15 labeled gases are shown in Table 1. These levels of impurities do not interfere with subsequent PET studies. Analysis of the gases is performed at least bi-weekly, and more often in times of heavy cyclotron usage. Increases in the amounts of impurities are then quickly noted and corrective measures (washing of system tubing, replenishment of charcoal in furnaces) promptly taken. As a routine procedure, the traps are replaced every week, and the charcoal level in the furnaces checked at the start of each week.

DISCUSSION

With the ever-increasing demand for routine production of positron-emitting radiopharmaceuticals, it has become necessary to design and construct remote or automated apparatus for their preparation. We and other have described, in detail, apparatus for the

production of several carbon-11 and fluorine-18 labeled radiopharmaceuticals(14-17). Apparatus for O-15 labeled radiopharmaceutical production is available from several commercial vendors of small medical cyclotrons. However, details of the construction and operation of these systems is not available, and the relibility of these apparatus over a long time span of heavy use is not well documented.

Methods for the transport of radiopharmaceuticals from a cyclotron to a PET facility have been recently described by other workers (18,19). The system described here is a modification of a system which has been in operation for many years. The apparatus for ^{15}O-H_2O production is entirely new, and replaced what had formerly been a manual procedure: this, in particular, has greatly reduced radiation exposure to personnel. The present system has been in continuous operation for more than a year, and for over 2000 radiopharmaceutical preparations. Typically, batches of 50-125 MCi of ^{15}O-H_2O, 200-300 mCi of ^{15}O-O_2, and 150-200 mCi of ^{15}O-CO are delivered to the PET imaging facility.

The entire system is controlled by the cyclotron operator who is seated at the cyclotron control desk. The steps in the production of each radiopharmaceutical are initiated by the operator and controlled by timing switches. The system in Figure 1 is located in the cyclotron vault, and the automatic bubbling apparatus located in a shielded hood in a separate room, 7 meters distant from the operator. Thus, the production of these radiopharmaceuticals is accomplished with virtually no radiation exposure to personnel. At present, the quality control analyses are performed manually in a separate chemical laboratory. We are currently installing an on-line gas chromatographic system, possibly microprocessor controlled, which can be used by the cyclotron operator to perform quality control checks at any time without disturbing radiopharmaceutical production.

There are several important features of this improved system. In the bubbling apparatus (Fig.2), the bubbling bag, syringe, tubing, etc., are all sterile and disposable. The entire equipment is then easily and quickly replaced for each new patient, eliminating problems with sterility and apyrogenicity of ^{15}O-H_2O samples sent to the PET facility. The bubbling apparatus can be used to prepare oxygen-15 labeled oxyhemoglobin and carboxyhemoglobin, by the bubbling of O-15 labeled oxygen or carbon monoxide (respectively) through a sample of blood placed in the bubbling bag. Finally, the production of all of the radiopharmaceuticals in the cyclotron laboratory, from whence they are sent to the PET imaging facility, has made it possible to furnish radiopharmaceuticals to multiple imaging devices: at present, there are two PET devices in our institution, and two more scheduled for installation in the near future. When all installed, there will be PET devices in three different buildings in the Washington University Medical Center, all supplied from one central cyclotron facility.

Acknowledgement. The work described here was supported by National Institutes of Health Grants HL13851 and NS06833. The authors thank William Margenau, Jack Robison, John Hood Sr. and Rollin Head for the design, construction and operation of this system, Mr. Keith Lechner for the quality control analyses, and Drs. M.E. Raichle and M.M. Ter-Pogossian for their continued interest in this project.

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