Impact of Yttrium-90 Microsphere Density, Flow Dynamics, and Administration Technique on Spatial Distribution: Analysis Using an In Vitro Model

Marcus Caine, MPhil, Michael S. McCafferty, BSc, Scott McGhee, MSc, Pedro Garcia, PhD, Wayne M. Mullett, PhD, Xunli Zhang, PhD, Martyn Hill, PhD, Matthew R. Dreher, PhD, and Andrew L. Lewis, PhD

ABSTRACT

Purpose: To investigate material density, flow, and viscosity effects on microsphere distribution within an in vitro model designed to simulate hepatic arteries.

Materials and Methods: A vascular flow model was used to compare distribution of glass and resin surrogates in a clinically derived flow range (60–120 mL/min). Blood-mimicking fluid (BMF) composed of glycerol and water (20%–50% vol/vol) was used to simulate a range of blood viscosities. Microsphere distribution was quantified gravimetrically, and injectate solution was dyed to enable quantification by UV spectrophotometry. Microsphere injection rate (5–30 mL/min) and the influence of contrast agent dilution of injection solution (0%–60% vol/vol) were also investigated.

Results: No significant differences in behavior were observed between the glass and resin surrogate materials under any tested flow conditions ($P = .182$; $n = 144$ injections). Microspheres tend to align more consistently with the saline injection solution ($r2 = 0.5712$; $n = 144$) compared with total BMF flow distribution ($r2 = 0.0104$; $n = 144$). The most predictable injectate distribution (ie, greatest alignment with BMF flow, $< 5\%$ variation) was demonstrated with $>$ 10-mL/min injection rates of pure saline solution, although $< 20\%$ variation with glass microsphere distribution was observed with injection solution containing as much as 30% contrast medium when injected at $>$ 20 mL/min.

Conclusions: Glass and resin yttrium-90 surrogates demonstrated similar distribution in a range of clinically relevant flow conditions, suggesting that microsphere density does not have a significant influence on microsphere distribution. Injection parameters that enhanced the mixing of the spheres with the BMF resulted in the most predictable distribution.

ABBREVIATIONS

BMF = blood-mimicking fluid, RHA = right hepatic artery, VFM = vascular flow model

Locoregional therapy of liver tumors with yttrium-90 (^{90}Y) radioembolization has emerged as a significant treatment option for patients ineligible for curative therapy (1). In ^{90}Y radioembolization, microspheres are injected into the hepatic arteries and mix with blood to be carried into the target tissue (2). Although ^{90}Y radioembolization has been performed since the 1960s (3,4), there is still significant debate on its

From the Department of Engineering and the Environment (M.C., X.Z., M.H.), University of Southampton, Highfield, United Kingdom; Biocompatibles UK (M.C., M.S.M., P.G., A.L.L.), Lakeview, Riverside Way, Watchmoor Park, Camberley, United Kingdom GU15 3YL; Biocompatibles (M.R.D.), West Conshohocken, Pennsylvania; and BTG International Canada (S.M., W.M.M.), Ottawa, Ontario, Canada. Received April 19, 2016; final revision received and accepted July 1, 2016. **Address correspondence to** M.C.; E-mail: marcus.caine@btgplc.com

M.C., M.S.M., P.G., and A.L.L. are paid employees of Biocompatibles UK (Farnham, United Kingdom), a BTG International company (West Conshohocken, Pennsylvania). S.M. and W.M.M. are paid employees of BTG International Canada (Ottawa, Ontario, Canada). M.R.D. is a paid employee of Biocompatibles. X.Z. and M.H. are employed by the University of Southampton and supervise a PhD research contract with Biocompatibles UK, a BTG International company.

Appendix A and Figures E1 and E2 are available online at *www.jvir.org*.

J Vasc Interv Radiol 2017; 28:260–268

http://dx.doi.org/10.1016/j.jvir.2016.07.001

technical considerations, including delivery technique and material (5). There are currently two commercially available microsphere products composed of resin (SIR-Spheres; Sirtex, North Sydney, Australia) and glass (TheraSphere; Biocompatibles UK, Farnham, United Kingdom), both of which comprise microspheres of similar size, but with different densities (resin, 1.6 g/cm^3; glass, 3.3 g/cm^3) (5–7). The difference in density has the potential to affect in vivo localization, although studies have shown no clinically relevant variation between anterior and posterior distribution of both material types (5,8). Uncertainty remains in regard to the mixing of the injected particles with the blood and their eventual distribution (2,9,10). The ability to predict microsphere distribution based on density and injection technique could enable enhanced dosimetry and ultimately treatment success (11,12).

The radiation dose from ^{90}Y microspheres is limited in range, with 50% of the absorbed dose within 2.5 mm of the microsphere (2). This necessitates final positioning of the microspheres close to their intended target and highlights the need for predicable distribution for maximum effect. Radioembolization is often administered in a proximal or lobar location, and it is an oversimplification to assume that the microspheres will mix homogeneously with the blood and then simply go wherever the blood goes, although this is often presented in flow-distribution studies (13,14). Factors thought to be significant for the prediction of distribution of microspheres include the size and density of the particles and the degree to which the particles will homogeneously mix with the blood during administration. When combined with technologies such as dynamic computed tomography (CT) for imaging of vascular flow to allow an administration tailored to the patient's hemodynamic characteristics (2), there is potential to improve dosimetric control.

The objective of the present study was to investigate material density, flow, and viscosity effects and their influence on microsphere distribution within an in vitro vascular flow model (VFM) designed to simulate flow conditions within hepatic arteries. The central hypothesis is that radioembolic surrogate density will affect flow distribution.

MATERIALS AND METHODS

Experimental Setup

The VFM used for the present study was a silicone vascular cast (Elastrat Sarl, Geneva, Switzerland) with circular channel cross-sections, a 4-mm inlet, and six 0.9-mm outlets (**Fig 1**) (15). The inlet diameter was chosen to represent the hepatic vasculature at a typical injection point for ^{90}Y microsphere therapy at the right hepatic artery (RHA), and the outlet diameter is akin to that of a first-order hepatic bifurcation (16,17).

The VFM was oriented in the vertical plane (ie, perpendicular to the bench) to test density/gravitational influence on distribution and in the horizontal plane to evaluate the injection mixing. Inlet length was selected to ensure a fully developed flow profile from the catheter injection point before the first bifurcation (calculation presented in **Appendix A** [available online at *www.jvir.org*]) (6,7,18–27).

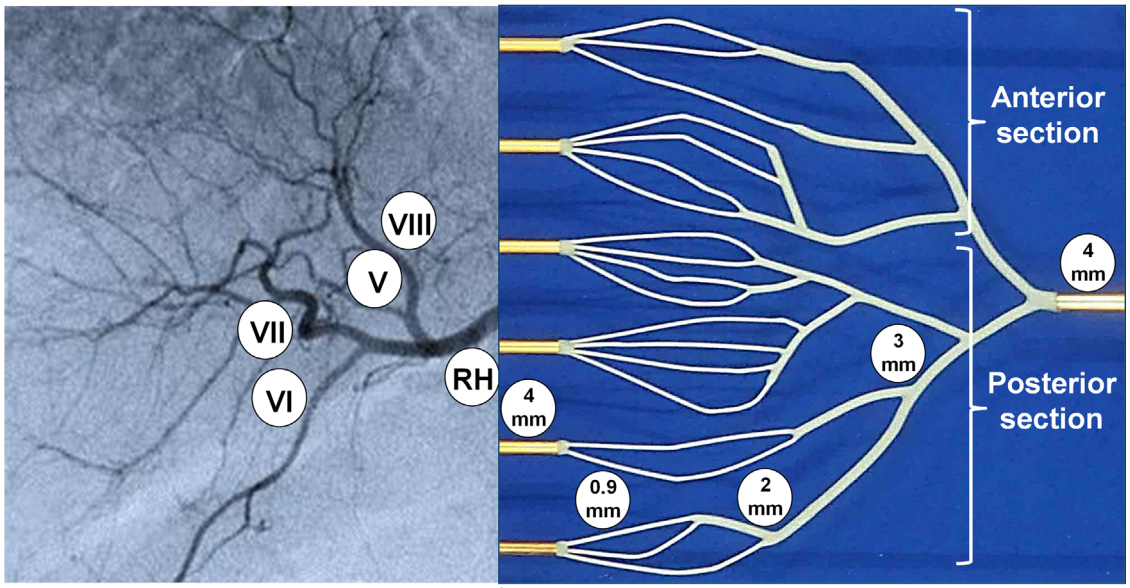

Figure 1. Comparison of **(a)** typical hepatic vasculature showing the RHA (*RH*) and the main arteries feeding liver segments V–VIII (angiogram adapted with permission from Kerlan [15]) and **(b)** VFM vessel orientation with anterior, posterior, and internal channel diameters labeled.