IMAGE-PLANE-DESTRUCTION EFFECTS ON ULTRASOUND CONTRAST DESTRUCTION-REPLENISHMENT CURVES

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Abstract

Image intensity as a function of microbubble refilling time, t, in a bubble-free zone (emptied by acoustic destruction) is currently fit to a bounded exponential, $I(t) = A(1-e^{-t/\tau})$, to assess local blood flow rate t and volume A. Observations *in vivo*, however, sometimes present an unexplained inflexion point in the initial refilling curvature (sigmoid shape) not described by this model which inhibits flow rate estimation based on the model. This work aims to experimentally reproduce exponential and sigmoid-shaped refilling curves under controlled conditions and identify the mechanism behind curve shape differences.

Introduction

Ultrasound contrast agents (USCAs), consisting of strongly reflecting gas microbubbles injected in solution intravenously, increase intensity of backscattered echoes from blood-filled regions of vascularized tissues. Because these microbubbles circulate at the same velocity as the ambient blood flow, remain in the vascular space and can be visualized in the microcirculation using nonlinear imaging techniques, they are very promising blood pool tracers [1 - 7].

Specific ultrasonic functional imaging sequences have been developed that can, in principle, allow to determine the blood exchanges in a volume of tissue by studying modifications in the intensity (related to microbubble concentration) of the signal from microbubbles. One recent approach to functional imaging is initiated by continuous injection of USCA. Once stable concentration of contrast in the blood pool is achieved, microbubbles are destroyed in a region of interest by applying a rapid series of high intensity acoustic pulses (imaging at high Mechanical Index). Following this, low acoustic power (imaging at low Mechanical Index) is used to observe refilling of microbubbles in the region while minimizing destruction. The intensity of the signal from reperfused microbubbles measured on these images as a function of time is referred to as the destruction-reperfusion or refilling curve.

Using measurements in myocardium, Wei et al [1] was the first to propose that the refilling curve could be described by a bounded exponential $I(t) = A(1-e^{-t/\tau})$ where $I(t)$ is the intensity of the signal from the microbubbles as a function of time, τ is related to the blood flow and A is related to the relative blood volume in the region (Figure 1). Other authors have applied this model to study renal [3, 4] and cerebral [5-7] blood perfusion.

However, in practice, this exponential model doesn't always fully describe the forms observed for the refilling curves. Several authors have observed destruction-reperfusion curves with a sigmoid form such as shown by the dashed line in Figure 1 with a low initial slope followed by an inflexion point. In particular, such curves have been observed in cerebral [5] and renal [3, 8] tissue.
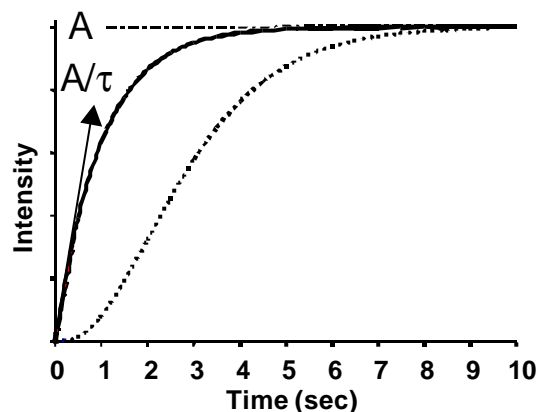

Figure 1 : The solid curve demonstrates the form of a destruction reperfusion curve following the bounded exponential form. In this case, the plateau level can be related to the relative blood volume **A** and the initial slope to the relative blood volume divided by the time for blood volume renewal τ. The dashed curve demonstrates the sigmoid form which has been observed in some cases.

This work proposes an explanation for such modifications in destruction-reperfusion curve forms and demonstrates that the proposed model corresponds well to experimental observations.

Methods

Mathematical model of destruction-reperfusion curves

If the region of interest (ROI) which is initially cleared of microbubbles at time $t = 0$ can be considered as a single mixed tank, the concentration of the microbubbles as a function of time $C(t)$ predicted according to indicator-dilution theory with

continuous infusion of C_0 microbubbles per liter from vessels that feed the ROI is described by:

$$\frac{dC(t)}{dt} = \frac{F}{V_b} C_0 - \frac{F}{V_b} C(t) - \lambda C(t) \qquad (1)$$

where F = liters of blood per second flowing in and out of the ROI, V_b = liters of blood in the ROI when full and λ = the fraction of microbubbles destroyed by the observational ultrasound beam per second. (If λ is set equal to zero, the solution to this equation corresponds to the bounded exponential form predicted by Wei et al with $C_0 = A$ and $V_b/F = t$.) Curves traced using the solution to the equation for nonzero λ show that the destruction due to observation lowers the plateau of the curve but that the slope at the origin is not changed. Thus, destruction during acoustic observation can inhibit good estimation of V_b but should not affect estimations of the flow rate or the initial shape of the curve.

The above supposes that the blood vessels entering the ROI were not themselves submitted to the destruction pulse. Consider now several sub-volumes in the insonified zone oriented serially with respect to the direction of flow. When the bubbles coming into the sub-volume **n** have already travelled under the ultrasound field in the sub-volume **n-1**, the number of bubbles entering the sub-volume **n** is itself a function of the output function of the sub-volume **n-1** (Figure 2). For the entry volume (n = 1), the solution to the equation describing these flow conditions is:

$$C_1(t) = \frac{C_0}{(1 + \tau\lambda)} \left[1 - e^{-\beta t} \right] \qquad (2)$$

where $\beta = (1 + \tau\lambda)/\tau$. When $\lambda = 0$, this equation again corresponds to the bounded exponential function proposed by Wei et al [1]. For subsequent sub-volumes (n > 1):

$$C_n(t) = \frac{C_0}{(1 + \tau\lambda)^n} \times \left\{ 1 - \left(1 + \sum_{i=1}^{n-1} \frac{\beta^i t^i}{i!} \right) e^{-\beta t} \right\}. \qquad (3)$$

This equation describes a curve with a low initial slope increasing secondarily until an inflexion point (sigmoid). The Figure 3 shows the microbubble concentration as a function of time following destruction as calculated using equation 3 with two flow rates and two sub-volume positions.
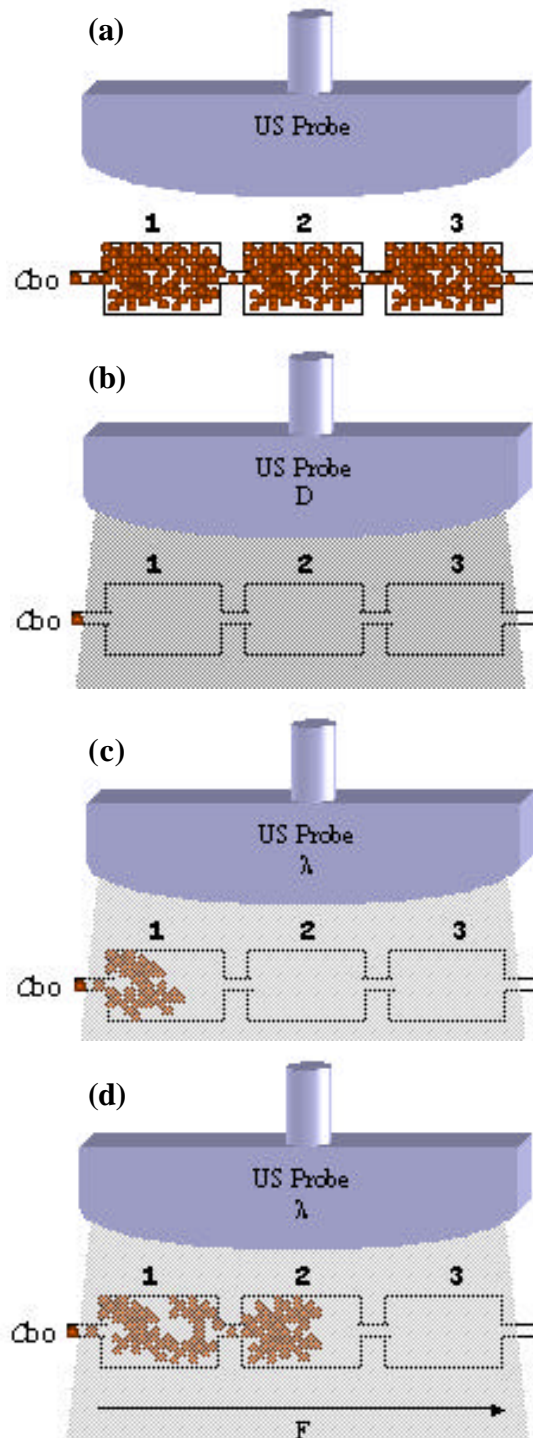

Figure 2 : Image plane perfused by vessels oriented along the same flow direction, F. (a) all compartments of the vascularization contain equal contrast concentration, C_{b0}, prior to ultrasonic investigation. (b) A destruction pulse, D, is applied, removing all microbubbles from the plane. (c) First observational image acquired at weak acoustic pressure such that only a small fraction of microbubbles λ are destroyed. The first compartment receives a concentration of C_{b0} microbubbles, but the second and third compartments do not have the same in-flow concentrations. (d) Later early-stage imaging plane, as the microbubble concentrations increase progressively at different rates in each compartment.
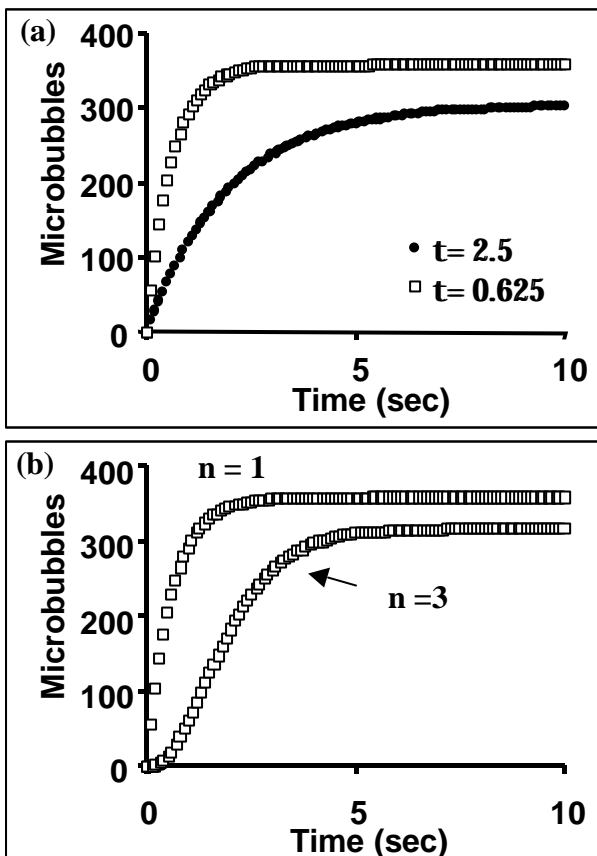
Figure 3 : Destruction-reperfusion curves calculated from equation (3). (a) Predictions in the first compartment (n = 1) at two different flow rates. (b) Predictions for the same flow rate in the first and third compartments. Reprinted from [8], copyright 2003, with permission from the RSNA.

Experimental measurements

Continuous injections of Sonovue microbubbles were made in a flow phantom containing ~9000 parallel, 200-μm hollow fibers (100, 200 and 400 ml/min) and in two rabbit kidneys *in vivo*. Image planes are shown in Figure 4. Non-linear gray scale images were acquired at low acoustic intensity (mechanical index = 0.08) after maximum image pressure was applied to destroy all bubbles in the image plane (HDI 5000, ATL-Philips). Destruction-replenishment curves of average gray scale intensity (HDI Lab) were compared for regions of interest (ROIs) placed where microbubbles first intersected the image plane (flow phantom inlet, segmental arteries of kidney) and ROIs placed at positions where imaged microbubbles had already traveled across part of the imaging plane (flow phantom outlet, kidney cortex).

Results

Refilling curves based on microbubbles just entering the image plane were well described by the model I(t) = A(1-e$^{-t/\tau}$) and initial slopes of these curves varied with flow rate in the phantom as predicted (Figure 5). Curves obtained at ROIs filled by microbubbles that

had already passed through the image plane exhibited a sigmoid shape (Figure 6). Thus, experimental data obtained at different image-plane positions and flow rates follows the behavior predicted by the mathematical model.
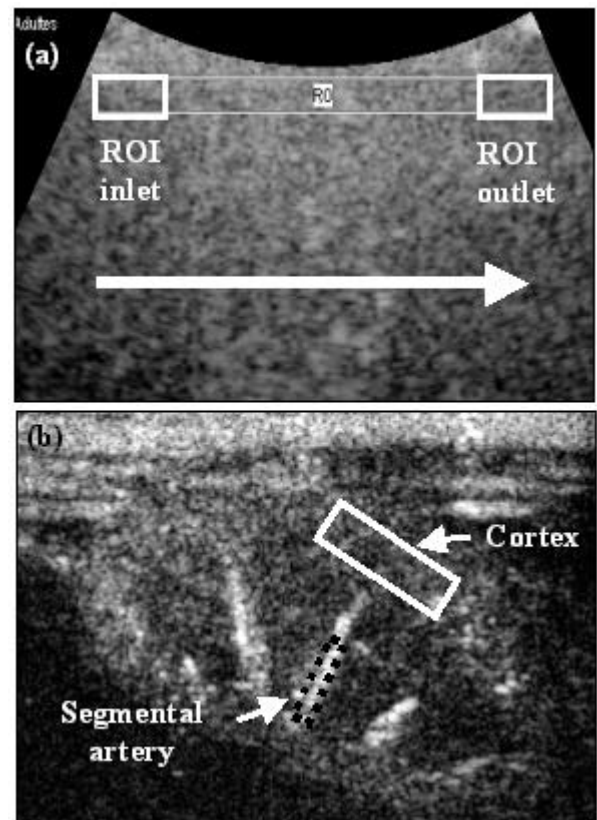

Figure 4 : (a) image plane in the flow phantom. Intensity was estimated in a ROI at the inlet and another at the outlet with respect to the direction of flow in the hollow fibers (white arrow). (b) image plane in rabbit kidney. ROIs were seleted in the segmental arteries near the hilum and in the cortex.

Conclusions

Our model shows that when the vessels that feed the ROI have previously been emptied of bubbles, the replenishment curve is no longer an exponential approaching a maximum but a sigmoid. Consequently, if microbubble destruction occurs in the feeding vessels, the microbubble velocity in the ROI estimated from the initial slope of the fit of the refilling curve to a bounded exponential is not correct. This effect is anticipated to be most important in tissues with well-organized terminal vascularisation. This work suggests, that it is best to minimize insonification of feeding arteries during destruction-reperfusion measurements in parenchyma and to limit the zone of microbubble destruction only to the studied zone. Such precautions should help obtain reliable and reproducible estimation of both the flow rate and the fractional blood volume of a selected organ.
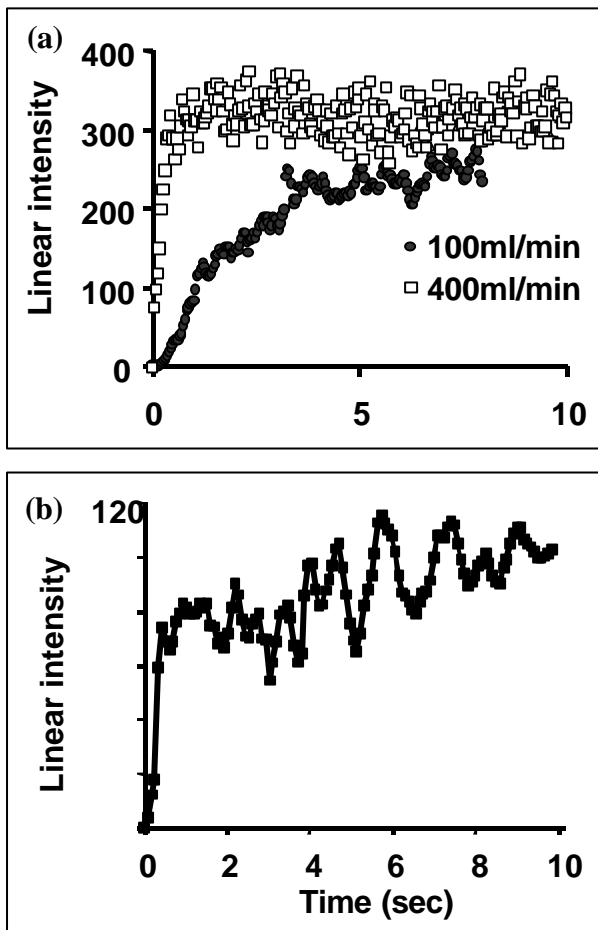
Figure 5 : Experimental destruction reperfusion curves obtained (a) in the ROI at the inlet of the flow phantom at two different flow rates. (b) in the segmental artery of rabbit kidney. As predicted by the model, these curves obtained in regions filled by microbubbles just entering the ultrasound field follow a typical bounded exponential form. Reprinted from [8], copyright 2003, with permission from the RSNA.
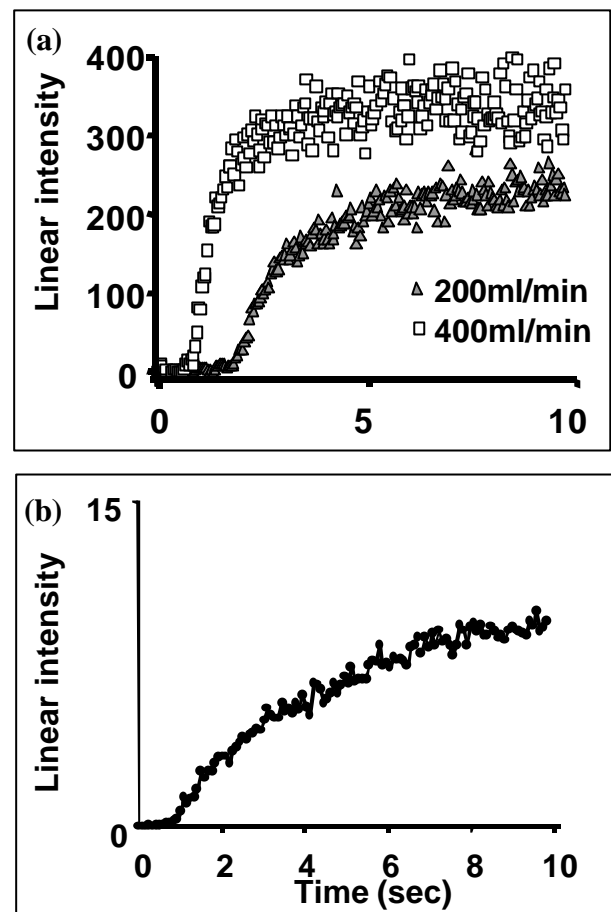

Figure 6 : Experimental destruction-reperfusion curves obtained (a) at the outlet of the flow phantom at two flow rates. (b) in the cortex of rabbit kidney. These curves, obtained from regions filled with microbubbles that have traversed regions of the destruction-plane, present the sigmoid shape predicted by equation (3) for a compartment far from the entry of microbubbles in the image plane. Reprinted from [8], copyright 2003, with permission from the RSNA.

References

[1] K. Wei et al, "Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered at a constant venous infusion," Circulation, vol. 97, pp. 473-483, 1998.

[2] D.H. Simpson et al, "Pulse inversion Doppler: a new method for detecting nonlinear echoes from microbubble contrast agents," IEEE Trans UFFC, vol. 46, pp. 372-382, 1999.

[3] T. Schlosser et al, "Feasibility of the flash-replenishment concept in renal tissue: which parameters affect the assessment of the contrast replenishment?," Ultra Med Biol, vol. 27, pp. 937-944, 2001.

[4] K. Wei et al, "Quantification of renal blood flow with contrast-enhanced ultrasound," J Am Coll Cardiol, vol. 37, pp. 1135-1140, 2001.

[5] S-J. Rim et al, "Quantification of cerebral perfusion with 'Real-Time' contrast-enhanced ultrasound," Circulation, vol. 104, pp. 2582-2587, 2001.

[6] G. Seidel and K. Meyer, "Harmonic imaging--a new method for the sonographic assessment of cerebral perfusion," Eur J Ultrasound, vol. 14, pp. 103-113, 2001.

[7] G. Seidel et al, "Evaluation of blood flow in the cerebral microcirculation: analysis of the refill kinetics during ultrasound contrast agent infusion," Ultra Med Biol, vol. 27, pp. 1059-1064, 2001.

[8] O. Lucidarme, S. Franchi-Abella, J-M Correas, S.L. Bridal, E. Kurtisovski, G. Berger, "Blood flow quantification with contrast-enhanced US: 'Entrance in the section' phenomenon-Phantom and rabbit study," Radiology, vol 228, pp. 473-479, 2003.