P. C. Ho [2009] Med. Hypotheses Res. **5**: 27–35.

HYPOTHESIS

Cyclic Flow and Patterns of Cardiovascular Disease: Dynamic Parallel with Natural Flow Systems

Paul C. Ho*

Division of Cardiology, Hawaii Region Kaiser Permanente, Honolulu, Hawaii, USA

Abstract. **The mammalian circulatory system has many parallel features with nature's flow systems like rivers. The cyclic blood flow due to arterial pulsatility is analogous to the cyclic seasonal flooding of rivers due to the repetitive melting snow and dry seasons. Along the banks of a "pulsating" river, sand bars and beaches have been noted to fluctuate in size depending on the seasonal flows. These fluctuating sandy sediment deposits at the river banks are comparable to the dynamic nature of calcific mineral deposits and atherosclerotic plaque development in arteries. Experimental models of the cardiovascular system have demonstrated a relationship between pulsatile flow phenomena and site-specific arterial calcification and atherosclerosis. Analogous to physiologic studies, the controlled flooding experiments at the Colorado River's Glen Canyon Dam have shown correlations between the magnitude, duration and frequency of cyclic floods and dynamic sand bar depositions along specific sites along the river banks. Understanding the dynamic parallels between the cardiovascular and the natural flow systems may help to gain insights into solutions for challenges occurring in the respective fields.**

Correspondence: Dr. Paul C. Ho, Division of Cardiology, Hawaii Region Kaiser Permanente, 3288 Moanalua Road, Honolulu, Hawaii 96819, USA. Tel: 808-432-7238. Fax: 808-432-8385. E-mail: paul.c.ho@kp.org.

Abbreviations used: **Author: Pleasea list any abbreviations here.**

Received on 03-26-2009; accepted on 05-18-2009.

1. Introduction

Pulsatility, oscillations or cyclic flow is a common feature of the mammalian cardiovascular system arising from mechanical actions of the beating heart. Perhaps not as obvious but also applicable, cyclic flow is found in other natural flow systems such as rivers. Cyclical nature of seasonal changes causes rivers to be flooded in the spring from melting snow and relatively low volume flow during dry seasons of the fall. Pulsatility and cyclic flow, though may vary in magnitude, duration and frequency, are ubiquitous across flow systems from the mammalian circulatory to natural ecological transport system.

As referenced throughout this study, numerous experimental observations are available to show that the addition of pulsatility or oscillations to steady flow can alter the global dynamics of the flow system affecting their geometric structure, flow dynamics, stress behavior and deposition pattern. A logical next question is whether the mammalian cardiovascular system would develop disease in similar fashion as observed clinically if the circulation were of more steady, and less pulsatile, flow? A similar question can also be asked about the natural flow systems: how would the landscape or structure of the flow system change with alterations in the cyclical pattern of seasonal flow? Understanding the effects of cyclic flow can lead to identifying it as a principal driver in cardiovascular disease development and natural flow system dynamics, and as such strategies to alter outcomes may have to include methods to ameliorate its downstream effects.

2. Methods and Results: Comparative Experimental Models

The formation and disappearance of sand bars along the Colorado River in the Grand Canyon of the United States have known to be significantly affected by damming at an upstream site by the Glen Canyon Dam and the subsequent controlled flooding experiments by periodic flow release from the dam [1]. Although different in the nature and mechanism, the pattern of sand bar deposition along the river mimics certain calcific deposition observed in the cardiovascular system which also depends on the periodic nature of pressure and flow of the system.

Cyclic flow reacts with geometric structure of the flow paths creating physical forces which can influence stress and deposition patterns of particulate matter. The altered deposits may in turn change the geometry and structure of the flow paths [2]. In this study, parallel features between biological and ecological flow systems are drawn from observations in *in vitro* flow experimental models, *in vivo* experimental models and experiments with controlled flooding at the Glen Canyon Dam. Special focus is made in the comparison of a specific pattern of cardiovascular calcification due to cyclic blood flow with sand bar deposition at the river bank due to periodic controlled flood releases.

2.1. *In Vitro* Flow Models

An idealized flow system consists of a perfectly symmetrical and linear conduit in steady state flow would generate a perfectly laminar, parabolic flow pattern with no disturbances [3]. Flow disturbance can be introduced when pulsatility and altered geometry are introduced into the system. A causal relationship between pulsatility and geometry, e.g., oscillatory flow at a branch point, aneurysm or atherosclerotic plaque, in turbulent flow has been suggested [2]. Shear stress fluctuations have also been observed by interactions of pulsatile flow conditions in bifurcations of *in vitro* models [4,5].

Other studies have been performed to compare steady and pulsatile flow conditions in casts of the arterial bifurcations. Compared to steady flow, pulsatility changes the flow pattern and angle of induced secondary flow at branch points [6]. Furthermore, pulsatile flow significantly increases the shear rates at the bifurcation when compared to steady flow [7]. Earlier mathematical simulations [8] have calculated significant enhancement of shear and flow separation at a branch point due to pulsatile flow, as later validated by these *in vitro* experimental observations. Cyclic nature of shear and flow

Equation 1:

$$\sigma_A = \frac{\sigma_A \left\{ 1 + \sum_{p=a}^{N} \Gamma_p \, e^{-2[(\alpha + j\beta)x]p} + \sum_{\substack{p=a \\ q \neq p}}^{N} \Gamma_p \Gamma_q \, e^{-2[(\alpha + j\beta)x]q-p} + \sum_{\substack{p=a \\ q \neq p \\ r \neq q \neq p}}^{N} \Gamma_p \Gamma_q \Gamma_r \, e^{-2[(\alpha + j\beta)x]r-q+p} + \ldots \right\}}{1 + \sum_{\substack{p=a \\ q \neq p}}^{N} \Gamma_p \Gamma_q \, e^{-2[(\alpha + j\beta)x]q-p} + \sum_{\substack{p=a \\ q \neq p \\ r \neq q \neq p \\ s \neq r \neq q \neq p}}^{N} \Gamma_p \Gamma_q \Gamma_r \Gamma_s \, e^{-2[(\alpha + j\beta)x]s-r+q-p} + \ldots}$$

alterations have been correlated to atherosclerosis in the arteries (see *in vivo* models below).

A specific mathematical model designed to calculate the physical stress induced at boundaries, e.g., changes in material and geometric properties, under pulsations [9] was constructed to study the locations and degrees of deposition of particulate and mineral matter. This theoretical model calculated for enhanced stress differentials (stress gradients) at sites of acute material property and geometric alterations (see *Equation 1*). In this equation, $\boldsymbol{\sigma_A}$ is the total stress observed at site A; σ_A is the initial stress condition at site A; $\Gamma_{\circledcirc}$is the coefficient for wave energy reflections based on boundary conditions of local material properties and geometry; (α + jβ) x is the product of the wave energy propagation coefficient and distance, e.g.., a = ($\alpha_{\circledcirc}$ + j$\beta_{\circledcirc}$) x_a. p, q, r, and s denote the influence of all upstream and downstream wave propagation coefficients and distances. As evident by *Equation 1*, the total stress observed at any location depends on the cyclic wave energy / flow interactions with all upstream and downstream structural boundaries and properties.

In vitro experimentation using mechanical vibrations pulsating through boundaries validated the results of the calculations. At predicted boundary sites of increased stress gradients due to oscillations, particulate deposits (FIG. 1) and calcific mineral deposits (FIG. 2) were observed to occur [10] as compared to controls without cyclic pressures and flow.

2.2. *In Vivo* Physiologic Models

Pulsatile flow has been hypothesized to be a critical modulator of the natural history of atherosclerosis [12]. *In vivo* experimental models using arterial bypass grafts have demonstrated that cyclic factors and pulsatility are associated with increased anastomotic intimal hyperplasia [13], vascular smooth muscle cell proliferation [14], and arterial geometric alterations such as dilatation and tortuosity [15]. In a human carotid arterial bifurcation model, positive correlation was made between cyclic flow, low oscillating shear stress and the development of local atherosclerosis [16]. Moreover, pulsatilility was found to be a powerful predictor of restenosis after

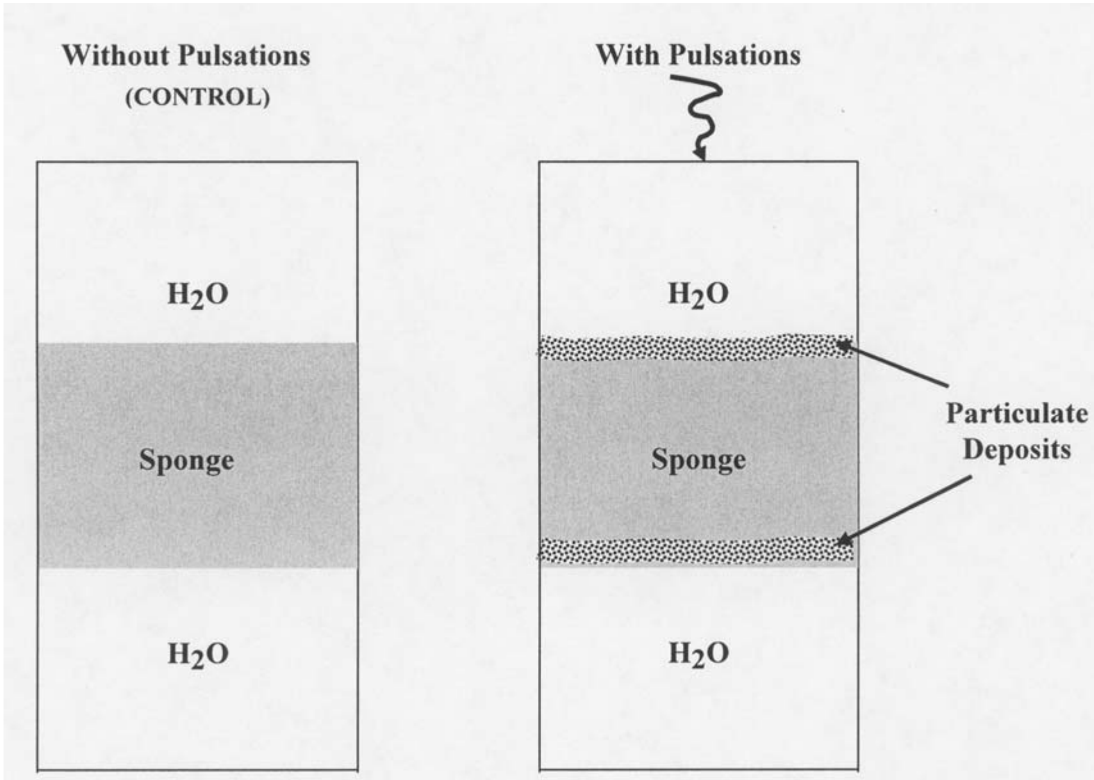

Figure 1. Schematic representation of the *in vitro* experiments using ink-particle markers as deposited by the stress gradients at the water-sponge boundaries induced by the pulsatile forces as predicted by the mathematical model.

percutaneous coronary angioplasty [17].

Another manifestation of cardiovascular disease, cardiovascular calcification, has also been associated with arterial pulsatility. As the mathematical model of pulsatility in a flow system predicted the locations of particulate and calcific mineral deposits in the *in vitro* observations [see *in vitro* flow models], when applied to an *in vivo* experimentation of tissue-patch ventricular patch implanted in the sheep's heart the model correctly predicted calcific mineral deposits within the bioprosthesis in location and relative amounts [9,18,19] (FIG. 3). Without pulsatility, the particulate deposition and calcific mineralization in the *in vitro* and *in vivo* experiments would not have occurred in the pattern as observed; in the *in vitro* experiments the particulate and calcific depositions did not occur at all in the controls with no pulsations. Cyclic factors such as arterial pulsations and oscillatory flow, therefore, can potentially have significant influence in all aspects of cardiovascular disease development.

2.3. Natural Ecological Systems

The Glen Canyon Dam of the Colorado River was built around 1963. Prior to the dam construction, the Colorado River experienced the natural seasonal variations of flow volume, sedimentation of the river bed and even water temperature [1]. Before the dam was built, the usual flow pattern of the Colorado River was at the highest in the springs due to the melting snow and at the lowest in late summers. The presence of the dam drastically changed the flow pattern of the river. The frequency and size of the seasonal floods were significantly reduced, and the amount of downstream sedimentation was limited [1]. The size and location of sand bars, beaches, cobbles and boulders along the river banks were altered as such the local ecosystem was significant effected. Concern for nega-

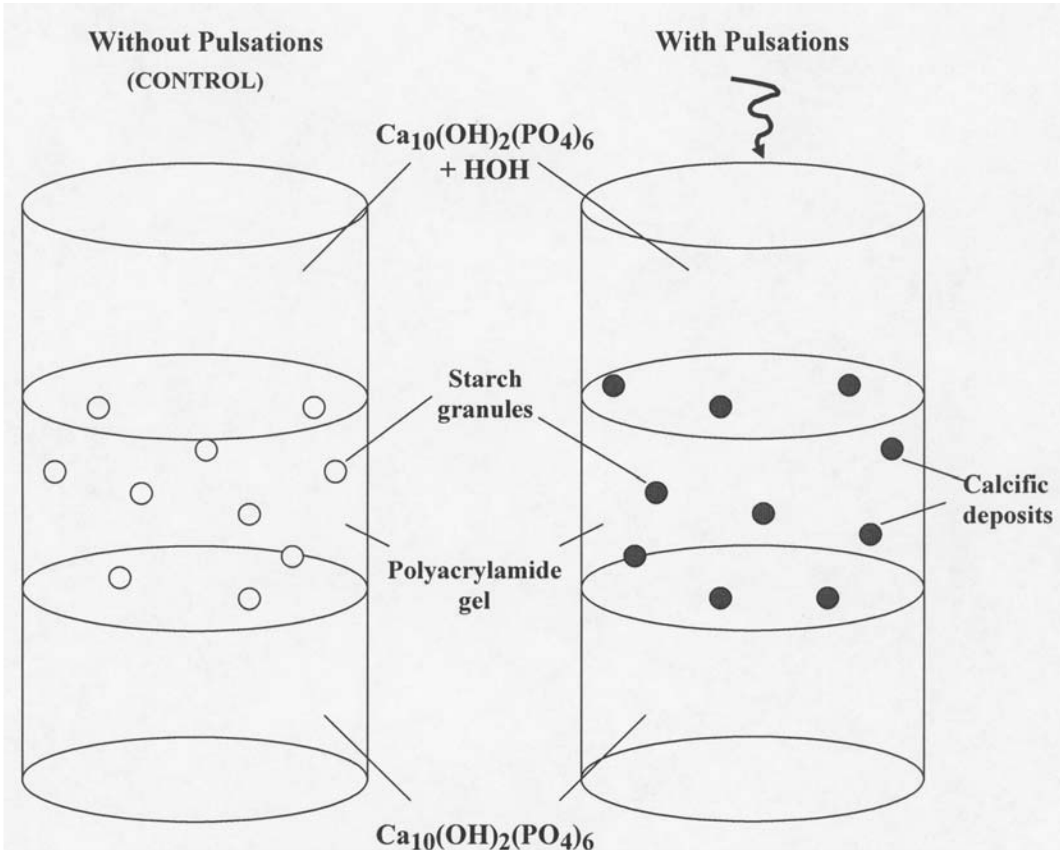

Figure 2. Schematic representation of the *in vitro* experiments using calcium and phosphate ions as mineral markers as deposited by the stress gradients at the polyacrylamide gel-starch granule boundaries induced by the pulsatile forces as predicted by the mathematical model.

tive environmental impact let to a series of experiments designed to restore the river ecology by periodic controlled flooding by water and sediment release at the dam (FIG. 4). A physiologic analogy would be as if the river was "pulsated" with cyclic flow as an attempt to restore a natural (and healthy) condition of the downstream environment.

The sand in the river basin is apparently not stationary, but undergoes constant movement dependent on the flow conditions. In quiescent flow, the sandy sedimentation move slowly downstream near the bottom of the river bed. During periods of high volume flow, the flooding can possess enough hydraulic energy to suspend the sandy particles and deposit them higher up in the river banks [1]. The sand bars and beaches created as such can sustain vegetation, animal life, and be used recreationally. The sand bars can further create eddies in the flow stream which develops into areas of low-flow habitats and ecosystem for fish development. Changes in the river bank geometry (or topography) will in turn alter the dynamics and patterns of the river flow [1]. Damming of the river significantly reduces the cyclic high volume flows and the amount of transported sedimentation to the downstream river system [1,20,21], which gradually led to the disappearance of the sand bars, beaches and low-flow habitats. As shown in the *in vitro* and *in vivo* experiments, parallel observations were recorded regarding cyclic flow and pulsatility's direct effects on the calcific deposits at certain boundary sites and local atherogenesis; in the absence of cyclic pressures and flow the specific particulate and calcific de-

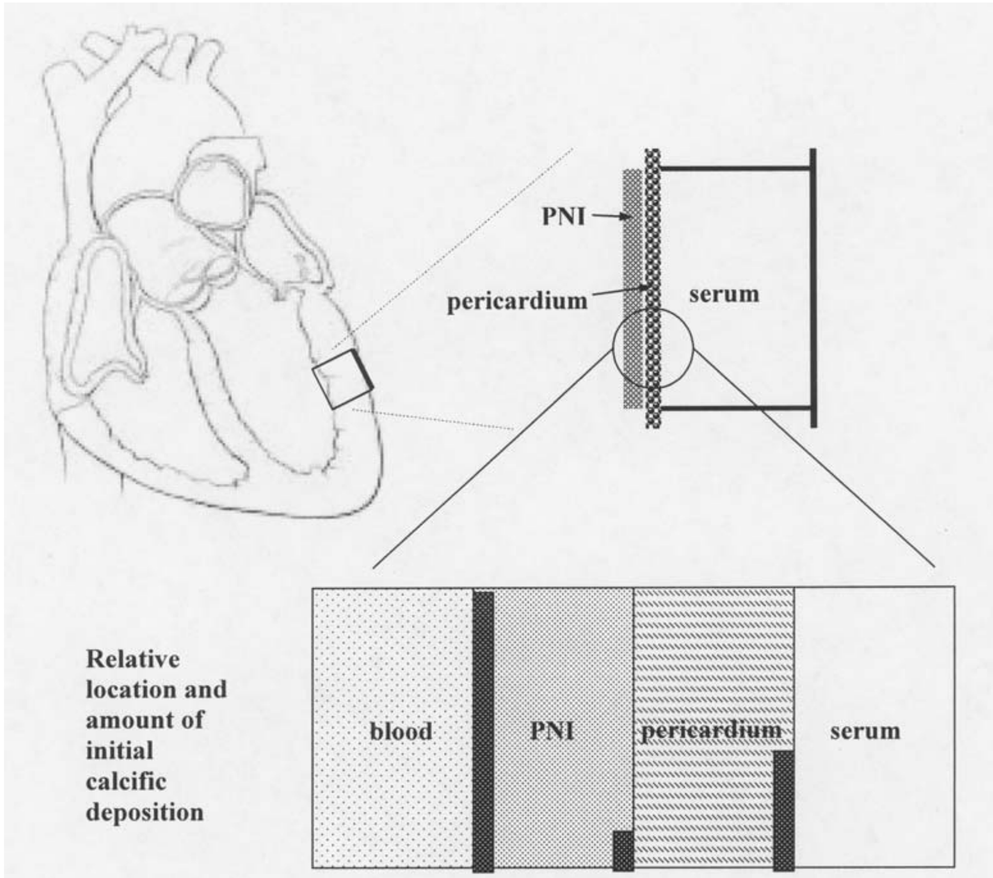

Figure 3. **Schmatic representation of the in vivo experiments using the implanted pericardial patch graft. Under the pulsatile forces of the beating heart, calcific mineralization (represented by Y) occurred at boundaries between blood–pseudoneointima (PNI), PNI-pericardium and pericardium-serum. The locations and relative amounts of calcific deposits were accurately predicted by the mathematical model.**

posits did not occur (FIG. 1 and 2).

The magnitude, duration and frequency of the controlled flooding were continuously studied even at present time [22-24]. Comprehensive understanding of the relationship between the magnitude, duration and frequency of the floods and optimal environmental impact is yet being determined. In general, however, flooding can provide transient high volume and high velocity water flow, and can deliver sandy sentiments to be deposited at the river banks as beaches and sand bars. The increased amount of sandy deposits at the river banks comes from the increased release from upstream environment, as well as increased updraft from the bottom of the river bed by the increased water velocity and turbulence from the floods. Sometime after the flooding, however, the sand bars would gradually washed off toward a lower deposition level. Another flooding would be necessary to increase and maintain the sand bar mass, and the amount of sand bar deposition can therefore be controlled by a pre-estimated duration, magnitude and frequency of controlled flooding by the dam (FIG. 5 and 6). Similar experimental designs in the circulatory system may yield valuable information regarding the control of cyclic flow and pulsatility with the potential for mitigation of cardiovascular disease pattern and behavior.

3. Discussion

Cyclic flow and pressure in the cardiovascular system is associated with disease development. Experimental models suggest that without pulsatility the flow pattern steadies and can

Figure 4. Color photograph of the controlled flooding experiment at the Glen Canyon Dam. (Photo by Bud Rusho, Bureau of Reclamation, 1984)

alter the pattern of cardiovascular disease such as the mitigation of calcific mineralization. In an analogous fashion, the Glen Canyon Dam serves as a damping structure for the seasonal cyclic floods in the river, and thereby, allowing for the sand bar to erode over time. The disappearance of the beaches at the river banks correlated with elimination of cyclic flow. Of note, the sand bar deposits at river banks may be desirable features of ecological health, however, calcific deposition in arteries is undesirable denoting disease development.

Cyclic flow interacts with the flow system's geometry which can lead to localized secondary flows, eddies and turbulence at specific sites such as at certain boundaries and bifurcations. In respective experiments, these specific locations have been correlated with the development of atherosclerosis and calcific deposition in the cardiovascular system, and sand bar deposition in the river system. For example, the observed sites of sand bar erosion and formation remained unchanged in the Colorado River, even though the degrees of flooding had been varied (FIG. 6). The intimate relationship between cyclic flow, geometry and material/particulate deposition is currently not well understood.

By varying the magnitude, frequency and duration of the test flows at the Glen Canyon Dam, important information regarding sand bar dynamics can be derived. Similar experimentation in the cardiovascular system would also yield important information on the relationship

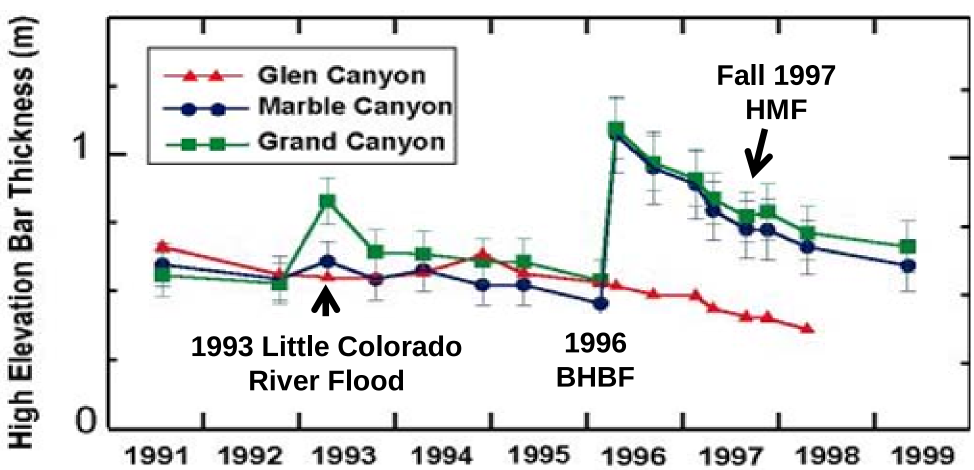

Figure 5. Plot showing changes in sand bar thickness as measured at various locations over time. The effects of various types of floods on the sand bar thickness are illustrated: beach/habitat-building flows (BHBF), habitat maintenance flows (HMF), and the little Colorado River flood was a naturally occurring event in 1993.

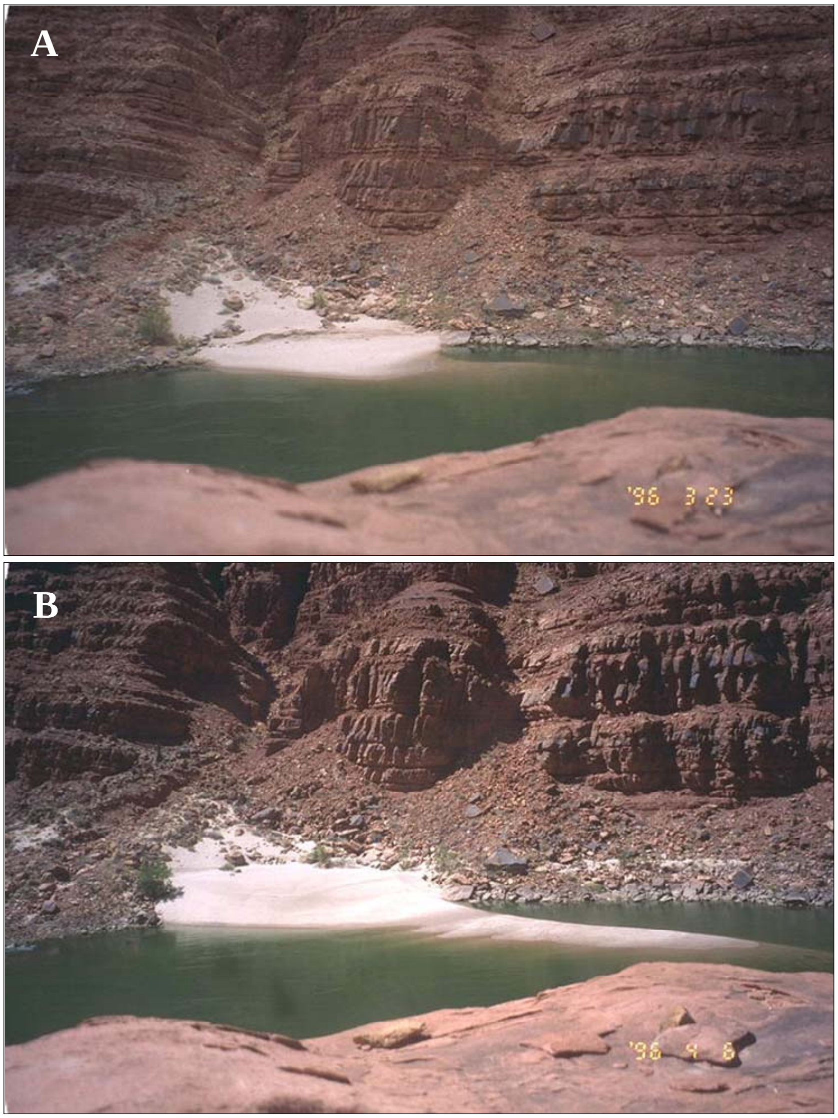

Figure 6. Photographic illustration of the disappearance and re-appearance of the beach at a study site: (A) pre-BHBF and (B) post-BHBF.

between cyclic flow and cardiovascular disease development. Conversely, surgical interventions of the cardiovascular system alter the geometry and boundaries of the flow system which can significantly impact the local interaction with cyclic flow. Perhaps ecologist may derive lessons from the medical experience as well in effectively controlling the river bank environment by artificial alteration of the flow path structure, eg., strategic placement of boulders creating boundaries to promote sand bar and low-flow eddy formation.

The cyclic flow of the cardiovascular system and the cyclic flooding of the river system draw parallel in the downstream effects of cardiovascular disease development and sand bar deposition, respectively. To study deeper into this analogy may be insightful to solutions for the respective challenges encounter in both areas of flow dynamics.

References

1. **Anderson MT, Graf JB and Marzolf GR.** Controlled flooding of the Colorado River in Grand Canyon: the rationale and data-collection planned. United States Department of the Interior and Geological Survey, Fact Sheet FS-089-96: http://water.usgs.gov/wid/FS_089-96/FS_089-96.html

2. **Ho PC, Melbin J and Nesto RW** [2002] Of geometry and compliance: Biomechanical perspective on vascular injury and healing. ASAIO J 48: 337-345.
3. **Nichols WW and O'Rourke MF** [1998] McDonald's blood flow in arteries, 4th edition, chapter 2, New York: Arnold Press.
4. **Weston MW, Rhee K, Tarbell JM** [1996] Compliance and diameter mismatch affect the wall shear stress distribution near an end-to-side anastomosis. J Biomech 29: 187-198.
5. **Kuban BD, Friedman MH** [1995] The effect of pulsatile frequency on wall shear in a compliant cast of a human aortic bifurcation. J Biomech Eng 117: 219-223.
6. **Deters OJ, Mark FF, Bargeron CB, Friedman MH, Hutchins GM** [1984] Comparison of steady and pulsatile flow near the ventral and dorsal walls of casts of human aortic bifurcations. J Biomech Eng 106: 79-82.
7. **Lutz RJ, Hsu L, Menawat A, Zrubek J, Edwards K** [1983] Comparison of steady and pulsatile flow in a double branching arterial model. J Biomech 16: 753-766.
8. **Friedman MH, O'Brien V, Ehrlich LW** [1975] Calculations of pulsatile flow through a branch: implications for the hemodynamics of atherogenesis. Circ Res 36: 277-285.
9. **Ho PC, Melbin J, Noordergraaf A** [1988] Local contributions to pulse transmission through heterogenous media. IEEE Trans Biomed Eng 35: 346-351.
10. **Ho PC, Melbin J** [2005] Mechanical vibration-driven particulate deposition and ionic mineralization at material boundaries in the fluid media. J Sound Vib 280: 1143-1147.
11. **Ho PC** [2007] The pulsewave reflections model: exploring a fundamental mechanism for cardiovascular calcification. Med Hypotheses 69: 792-799.
12. **Chatzizisis YS, Giannoglou GD** [2006] Pulsatile flow: a critical modulator of the natural history of atherosclerosis. Med Hypotheses 67: 338-340.
13. **Keynton RS, Evancho MM, Sims RL, Rodway NV, Gobin A, Rittgers SE** [2001] Intimal hyperplasia and wall shear in arterial bypass graft distal anastomoses: an in vivo model study. J Biomech Eng 123: 464-473.
14. **Grigioni M, Daniele C, D'Avenio G, Formigari R, Bernucci P, Ballerini L, Barbaro V** [2001] Pulsatile flow and atherogenesis: results from in vivo studies. Int J Artif Organs 24: 784-792.
15. **Sho E, Nanjo H, Sho M, Kobayashi M, Komatsu M, Kawamura K, Xu C, Zarins CK, Masuda H** [2004] Arterial enlargement, tortuosity, and intimal thickening in response to sequential exposure to high and low wall shear stress. J Vasc Surg 39: 601-612.
16. **Ku DN, Giddens DP, Zarins CK, Glagov S** [1985] Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. Arteriosclerosis 5: 293-302.
17. **Nakayama Y, Tsumura K, Yamashita N, Yoshimaru K, Hayashi T** [2000] Pulsatility of ascending aortic pressure waveform is a powerful predictor of restenosis after percutaneous transluminal coronary angioplasty. Circulation 101: 470-472.
18. **Frasca P, Buchanan JW, Soriano RZ, Dunn JM, Marmon L, Melbin J, Buchanan SJ, Golub EE, Shapiro IM** [1985] Morphological observations of mineralizing pericardium cardiac grafts. Scan Electron Microsc, Part 3, pp. 1253-1258. (citation correct?)
19. **Frasca P, Buchanan JW, Soriano RZ, Dunn JM, Marmon L, Melbin J, Buchanan SJ, Chang SH, Golub EE, Shapiro IM** [1984] Mineralization of short-term pericardial cardiac patch grafts. Scan Electron Microsc, Part 2, pp. 973-977.
20. **Topping DJ, Rubin DM, Vierra LE** [2000] Colorado River sediment transport: Part 1: Natural sediment supply limitation and the influence of Glen Canyon Dam. Water Resources Research 36: 515-542
21. **Topping DJ, Rubin DM, Nelson JM, Kinzel PJ, Corson IC** [2000] Colorado River sediment transport: Part 2: Systematic bed-elevation and grain-size effects of sand supply limitation. Water Resources Research 36: 543-570.
22. **Kaplinski M** [1999] Monitoring fine-sediment storage of the Colorado River ecosystem below Glen Canyon Dam. Northern Arizona University, Flagstaff, Arizona. http://www4.nau.edu/geology/namdor/sbarref.html
23. **Hazel J, Kaplinski M, Parnell R, Manone M** [2000] Monitoring the effects of the 1997 Glen Canyon Dam test flow on Colorado River ecosystem sand bars. Northern Arizona University: Sand Bars Studies Fact Sheet 2000. http://www.gcmrc.gov/files/pdf/fact_sheet_parnell_2000_2.pdf
24. **Hazel J, Kaplinski M, Parnell R, Manone M** [2001] Monitoring the effects of the spring 2000 habitat maintenance flow on Colorado River ecosystem sand bars. Northern Arizona University, Flagstaff, Arizona 2001. http://www.gcmrc.gov/files/pdf/fact_sheet_parnell_2001_3.pdf