A finite difference model of O₂ transport in aortic valve cusps: importance of intrinsic microcirculation

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Submitted 10 April 2003; accepted in final form 14 July 2003

Filion, Renee J., and Christopher G. Ellis. A finite difference model of O₂ transport in aortic valve cusps: importance of intrinsic microcirculation. Am J Physiol Heart Circ Physiol 285: H2099–H2104, 2003. First published July 17, 2003; 10.1152/ajpheart.00330.2003.—Recent studies have reported the presence of a microcirculation within the tissue of aortic valves. To test the hypothesis that this vascular bed is needed to satisfy the oxygen demands of the cusp tissue, a two-dimensional (2D) finite difference model of oxygen diffusion was developed. The in vivo environment was modeled for vascular and avascular cusps using thickness data from precise radiographic measurements of fresh porcine valves, and O₂ diffusivity (DO₂) and O₂ consumption (VO₂) values from experimental data. The location and density of the cusp vasculature were determined by the model to prevent oxygen levels from falling to zero. Validation of the model was performed by simulation of the experimental measurements of cusp DO₂ and VO₂. For a test cusp with uniform thickness, the model returned simulated DO₂ and VO₂ measurements within 1.43% and 0.18% difference of the true parameter values, respectively. For native cusps, the simulated DO₂ measurements were sensitive to thickness variations (~38 to +21% difference), whereas the VO₂ measurements were minimally affected (~8% difference). An improved DO₂ measurement technique was found to reduce these errors to ~5% and is recommended for analysis of experimental data. In the avascular case, the model predicted large regions of hypoxic tissue, whereas in the vascular case, the model predicted vessel locations and densities similar to what was experimentally observed in porcine cusps. Overall, the in vivo model developed in this study confirmed the need for an intrinsic microcirculation in the thicker basal regions of aortic cusps.

avascular; vascular; oxygen diffusivity; oxygen consumption rate; heart failure

The design of replacement valves relies on a clear understanding of the characteristics of the native valve that influence its function and durability. One of the main characteristics that influences the ability of the tissue to repair structural damage, and hence determines the durability of the native valve, is tissue oxygenation. How much O₂ does the valve tissue require and where does this oxygen come from?

Weind et al. (15) reported that most aortic valves have an intrinsic microcirculation located predominately in the thicker basal regions of the cusps. They speculated that this microvascular source of O₂ was necessary for tissue repair. In a separate study, Weind et al. (16) found that a microvascular bed was present in regions of the cusp where tissue thickness exceeded 0.5 mm, further supporting the possibility that diffusion of O₂ from the luminal blood is unable to completely satisfy the O₂ demands of the tissue. Weind et al. (14) measured the O₂ diffusivity (DO₂) and the O₂ consumption rate (VO₂) of porcine aortic valve cusps and predicted, based on a simple one-dimensional diffusion model, that an intrinsic microcirculation was necessary to prevent tissue hypoxia.

Current biological replacement valves do not have an intrinsic microcirculation. Whether or not the native valves require an intrinsic microcirculation to provide additional O₂ to the thicker regions of the cusps is an important consideration in the design of future, more durable, replacement valves.

This study aimed to improve understanding of the pathways for delivering O₂ to aortic valve cusps. To test the hypothesis that the vascular bed found in the thicker basal region of an aortic cusp is needed to satisfy the O₂ demands of the tissue, a two-dimensional (2D) finite difference model of O₂ diffusion through a user-specified cusp was developed. This model used experimentally derived data for cusp thickness as well as for DO₂ and VO₂. A unique feature of this model is the prediction of the location and density of the microcirculation needed to prevent regions of cusp tissue from becoming hypoxic.

METHODS

Finite difference model: in vivo stimulation. The model developed in this study considers DO₂ and VO₂ within the 2D...
centerline cross section of an aortic cusp, as shown in Fig. 1. The goal was to develop a model that would simulate the in vivo environment for a user-specified cusp, providing both avascular and vascular PO2 predictions for the cross section of valve tissue.

Clearly, O2 diffuses through an aortic valve in three dimensions. However, it was assumed for simplicity that the PO2 profiles of adjacent cross sections are similar. On the basis of this assumption, the flux of O2 between successive cross sections was neglected.

**Governing equations.** From Fick’s law of diffusion and the principle of mass balance, the differential equation describing unsteady-state 2D diffusion in an O2 consuming tissue is given by

\[
\frac{\partial P}{\partial t} = D \left( \frac{\partial^2 P}{\partial x^2} + \frac{\partial^2 P}{\partial y^2} \right) - \frac{V_{O2}}{k} \tag{1}
\]

where \(\frac{\partial^2 P}{\partial x^2}\) and \(\frac{\partial^2 P}{\partial y^2}\) are the second-order partial derivatives of partial pressure P with respect to x and y, P is PO2, and k is the O2 solubility of the tissue.

Equation 1 was solved numerically for the complex geometry of a cusp cross section using the explicit forward-time central-space finite difference scheme. The cusp cross section was represented as a collection of small square nodes of equal size, and the PO2 profile of the cross section was calculated at every time step based on the PO2 profile of the cross section at the previous time step.

**Valve geometry and three-layer structure.** The modeled cusp cross section was assembled from a thickness map of a real porcine cusp obtained by Weind et al. (17). Because this thickness map was obtained from a cusp lying flat on a supporting surface, it does not represent the exact shape of a cusp in vivo in either the relaxed (open) or stressed (closed) configuration, the top portions of the cusps are in contact with each other with similar PO2 levels and so no O2 flux occurs when the valve is closed (the 0 flux when the valve is open and a zero O2 flux when the valve is closed (the coaptation regions of the three cusps are pressed up against one another). This contact area is called the coaptation region and is thought to be composed almost entirely of the ventricularis layer. The presence of the coaptation region is included in the model and is characterized by the fraction of the total cusp height that it occupies, starting from the free edge. The size and location of the coaptation region within the modeled cusp cross section is shown in Fig. 2. It is assumed that only the ventricularis is present within the coaptation region.

**Boundary conditions.** The aortic valve is situated between the left ventricle and the aorta. Because blood returning from the lungs is pumped from the left ventricle into the aorta, it is assumed that the surrounding luminal blood is fully oxygenated. Furthermore, because it was experimentally shown that a high concentration of vessels is present at the base of the aortic valve (13), the tissue at the base of aortic valve is assumed to be fully oxygenated. These boundary conditions are implemented by surrounding the modeled cusp cross-section with well-oxygenated blood and tissue set at a constant PO2 of 100 mmHg.

The free edge of the cusp is treated separately. There are two possible boundary conditions: a nonzero O2 flux when the valve is open and a zero O2 flux when the valve is closed (the coaptation regions of the three cusps are pressed up against each other with similar PO2 levels and so no O2 flux is expected). This model assumes the worst-case scenario by approximating the cusp as if the valve were closed at all times, thereby implementing a zero-flux boundary condition at the free edge.

Necrosis is another important consideration in the model. To simulate the real-life situation where a lack of O2 results in cell death, the VO2 of nodes in the avascular case that reach a PO2 of zero are reset to zero. The necrotic cells are no longer consuming O2; however, O2 is still diffusing through the tissue.

In the vascular model, vessels are positioned on a need basis to avoid developing necrotic regions within the tissue. If the PO2 of any node within the cusp cross section drops below an arbitrary threshold of 2 mmHg, a vessel is positioned at the point of lowest PO2. The PO2 profile of the cusp cross section is recalculated after the addition of every vessel.
Model parameters. The parameters of the model and their default values are provided in Table 1. The geometric parameters of the model include the user-specified thickness map, the distance between successive thickness measurements, the node size, the fractional thickness of the individual layers, and the fractional size of the coaptation region. The default thickness map thicknessmap.txt was obtained via high-resolution digital radiography by Weind et al. (14). This thickness map corresponds to the thickness measured along the centerline of a porcine cusp from the free edge to the base. The successive thickness measurements are separated by a distance of 0.005 cm. A default node size of 0.005 cm × 0.005 cm is assumed based on reasonable computation time and desired model resolution.

Because steady state can never be fully achieved with the use of numerical solving techniques, a termination condition of \( \leq 0.0001 \) mmHg difference between all previous and current time step Po2 values is implemented. When this termination condition is satisfied, the cusp cross section is said to have reached pseudo steady state.

Layer thicknesses for the fibrosa, spongiosa, and ventricularis of 30%, 50%, and 20% of the total cusp thickness, respectively, are assumed (10). On the basis of Weind et al.’s (16) experimental observations, 20% of the total cusp height starting from the free edge is attributed to the coaptation region.

The cusp cross section is initially set at a uniform Po2 of 50 mmHg. Because the majority of vessel diameters reported by Weind et al. (15) are \(<20 \mu m\), with the occasional arteriole or venule having a diameter of up to 100 \(\mu m\), all vessels in the model are set at a constant Po2 of 50 mmHg. This Po2 level corresponds to a plausible Po2 value for a capillary bed.

The diffusivities of the individual layers are assigned according to Weind et al.’s (14) experimental measurements of Do2 in porcine cusps. The cusp is also assumed to have a uniform Vo2, assigned according to Weind et al.’s experimental measurements of Vo2 in porcine cusps. Furthermore, the cusp is assumed to have a uniform O2 solubility equal to 90% that of plasma at 37°C (4). The external blood is assumed to have diffusivity and solubility values equal to those of plasma at 37°C (9, 4, 16).

A graphical user interface was developed to facilitate customization of the model to a specific cusp. All parameters listed in Table 1 can be modified before running a simulation, including the thickness map of the cusp under consideration.

Simulation of experimental Do2 and Vo2 measurements. Simulations of the experimental measurement of cusp Do2 and Vo2, as performed by Weind et al. (14), were carried out to test the model and to explore the impact of variations in cusp thickness on Do2 and Vo2 measurements. Four cases were simulated: 1) a rectangular cusp with uniform Do2 to validate the model itself, 2) a notched rectangular cusp to explore the impact of thickness variability on the resulting Do2 and Vo2 measurements, and cusps with Weind et al.’s experimental thickness data but with either 3) uniform Do2 values, or 4) three layers with the in vivo model parameters to determine whether the spongiosa layer influences the impact of tissue thickness variability on Do2 measurements. Because the dissected cusps in Weind et al.’s experiments were not perfused, the cusps in these model simulations were avascular with a zero-flux boundary condition along the bottom ventricularis surface, which was in contact with glass. The Clark O2 sensor output in Weind et al.’s experiments was simulated by averaging the Po2 over its reported effective area of 300 \(\mu m\) centered on a sensor node positioned at the glass surface. The initial condition for both the Do2 and Vo2 simulations was the steady-state O2 levels in the modeled cusp with the other surfaces not in contact with the glass exposed to a fixed gas Po2. For the Do2 simulation, the sensor node Po2 output was stored for the transient response to a step change in gas Po2. For the Vo2 simulation, the sensor output was recorded for the transient response to imposing a zero flux condition at all exposed surfaces. The Do2 and Vo2 values for these simulations were obtained by fitting trend lines to the sensor data and performing the calculations outlined by Weind et al. (14) using

\[
\text{Do2} = \frac{4 \cdot L^2}{\pi^2 \cdot \tau}
\]

and

\[
\text{Vo2} = -k \cdot \frac{\Delta P}{\Delta t}
\]

where \(\tau\) is the time constant of the transient and \(\Delta P/\Delta t\) is the fall of Po2 over time. Weind et al. determined L from the mean thickness of the cusp over the effective sample range of the O2 sensor.

Software. All required programming, including the development of a graphical user interface, was performed with the use of Matlab version 6.0 (The MathWorks; Natick, MA).

RESULTS AND DISCUSSION

Simulation of experimental Do2 and Vo2 measurements. The rectangular cusp model with uniform thickness and uniform Do2 throughout returned simulated Do2 and Vo2 measurements within 1.43% and 0.18% difference, respectively, of the true parameter values.

**Table 1. Model parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Default Value</th>
<th>Reference</th>
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<td>Node size, (\mu m)</td>
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<td>S thickness fraction</td>
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<td>10</td>
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<td>V thickness fraction</td>
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<td>10</td>
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<tr>
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<td>9,16</td>
</tr>
<tr>
<td>V diffusivity, (cm^2 \cdot s^{-1})</td>
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<td>External diffusivity, (cm^2 \cdot s^{-1})</td>
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<tr>
<td>F solubility, ml O2/ml tissue (-1 \cdot mmHg^{-1})</td>
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<td>16</td>
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F, fibrosa; S, spongiosa; V, ventricularis.

AJP Heart Circ Physiol • VOL 285 • NOVEMBER 2003 • www.ajpheart.org
Thus the model for a uniform rectangular cusp was assumed valid and reliable.

The cross section of a native cusp, however, is irregular in geometry with drastic variations in thickness. Because the transient changes in \( \text{PO}_2 \) associated with the \( \text{DO}_2 \) simulations depend on \( L^2 \) (Eq. 2), the thicker region of tissue near the sensor should slow the transient response in our 2D simulation leading to an underestimation of the predicted \( \text{DO}_2 \) values. \( \text{VO}_2 \) measurements are independent of the tissue thickness (Eq. 3) and should be minimally influenced by thickness variations in our simulations. The model of a rectangular cusp with a notch of variable width centered on the sensor node confirmed that \( \text{DO}_2 \) measurements are very sensitive to thickness variations in the neighborhood of the sensor, whereas \( \text{VO}_2 \) measurements are not (Fig. 3).

The final two \( \text{DO}_2 \) and \( \text{VO}_2 \) simulations used the native valve thickness map with the simulated \( \text{PO}_2 \) sensor placed at five different locations (thin, thick, and transition from thin to thick tissue). Simulated \( \text{DO}_2 \) measurements for the cusp with a uniform diffusivity varied from \(-16\) to \(+20\)% difference from the true parameter value, whereas the three-layered cusp with the spongiosa generated a greater scatter, from \(-38\) to \(+21\)% difference. Because the same thickness profile, effective \( \text{DO}_2 \) values, and sensor positions were used in both simulations, these results demonstrated that the distinct layers of a composite cusp have an effect on the \( \text{DO}_2 \) measurements. It is speculated that the spongiosa, having a higher \( \text{DO}_2 \) and occupying a greater portion of the total cusp thickness, enabled \( \text{O}_2 \) to exchange more rapidly than the other two layers and hence exacerbated the impact of thickness variations.

The three-layer model returned measured \( \text{DO}_2 \) values between \( 6.59 \times 10^{-6} \) and \( 1.29 \times 10^{-5} \text{ cm}^2/\text{s} \), depending on sensor position. Weind et al. (16) reported experimental \( \text{DO}_2 \) measurements for porcine cusps that ranged from \( 7.7 \times 10^{-6} \) to \( 1.27 \times 10^{-5} \text{ cm}^2/\text{s} \). On the basis of the similarities between the simulation and experimental results, it is possible that the \( \text{DO}_2 \) measurements obtained by Weind et al. did not properly account for the thickness variations in native cusps. Weind et al. used the mean cusp thickness in the assumed effective area of the sensor. However, because the time course for the transient response to a step change in \( \text{O}_2 \) depends on \( L^2 \), the thickness should be computed from the root-mean-squared equation

\[
L_{\text{average}} = \sqrt{\frac{\sum L_i^2}{N}}
\]

where \( L_i \) is the thickness of the cusp at each measurement location and \( N \) is the total number of thickness measurements in the averaging region.

Equation 4 was applied to the notched rectangular cusp to obtain a new mean cusp thickness and, subsequently, to calculate a new value for \( \text{DO}_2 \). The averaging region was also increased from \( 300 \) to \( 600 \mu\text{m} \), centered on the \( \text{O}_2 \) sensor. New \( \text{DO}_2 \) values were obtained within \( 5\% \) of the true parameter value for all notch sizes considered. Thus, with the use of a more appropriate measure of the mean cusp thickness, it was possible to correct for the large scatter in the \( \text{DO}_2 \) measurements. Further studies are required to determine how large an averaging region is necessary for accurate \( \text{DO}_2 \) measurements. As a first approximation, an averaging region with a diameter at least as great as the largest thickness in the cusp cross section is proposed.

Although individual \( \text{DO}_2 \) measurements made by Weind et al. may be in error, the mean \( \text{DO}_2 \) reported by Weind et al. should be a good estimate of the true \( \text{DO}_2 \) for the aortic valve. This mean \( \text{DO}_2 \) was used for the following simulation of the native cusp in vivo.

Cusp oxygenation. The 2D finite difference model developed in this study was used to speculate on the need for an intrinsic microcirculation within native aortic valve cusps. A realistic representation of the centerline cross section of a porcine cusp was created based on a thickness map provided by Weind et al. (14). All model parameters were set to their default values outlined in Table 1. The model results are shown in Fig. 4 and Fig. 5.

Figure 4 displays the modeled cusp cross section in the avascular case (Fig. 4A) and in the vascular case (Fig. 4B). Notice the presence of the three layers and the coaptation region in both cases. The small black markings in the vascular cusp cross section correspond to vessels systematically positioned on a need basis to avoid the development of necrotic regions. A total of 21 vessels were positioned within the cusp: 16 vessels in the spongiosa of the basal region and 5 vessels outside the basal region.

In their experimental study, Weind et al. (16) observed that most aortic cusps have an intrinsic microcirculation located predominately in the spongiosa of the basal region. They also found a significant correlation between tissue thickness and vessel density (16). The results from the model presented in this study
support these observations. A high vessel density was found in the thicker basal region of the vascular cusp cross section, whereas a low vessel density was found outside the basal region. Except for a few vessels in the coaptation region, all vessels were positioned within the spongiosa. Specifically, Weind et al. (15) determined mean vessel densities of $3.98 \pm 5.21$ and $0.29 \pm 0.59$ vessels/mm$^2$ within and outside the basal regions of the cusps, respectively. The model developed in this study obtained vessel densities that fall within these experimental ranges: $4.78$ and $0.75$ vessels/mm$^2$ within and outside the basal region of the cusp, respectively.

Figure 5 displays the predicted $P_O_2$ profile of the cusp cross section at pseudo steady state in the avascular case (Fig. 5A) and in vascular case (Fig. 5B). Notice the large necrotic regions that developed in the avascular case. The onset of necrosis was prevented in the vascular case by the systematic positioning of small vessels on a need basis. Clearly, diffusion of $O_2$ from the luminal blood alone was unable to completely satisfy the $O_2$ demands of the tissue. These model results support the hypothesis that the vascular bed found in the thicker basal region of a native aortic cusp is needed to satisfy the $O_2$ demands of the tissue. In conclusion, the 2D finite difference model developed in this study was able to predict vessel locations and densities that agree with the experimentally observed vessel locations and obtained vessel densities (16) using thickness, $V_{O_2}$, and $D_{O_2}$ values from Weind et al. (14). The results from this model support the hypothesis that a microcirculation is needed to satisfy the $O_2$ demands of the thicker regions of the native aortic valve cusps.

Simulation of experimental $V_{O_2}$ and $D_{O_2}$ measurements revealed that variations in cusp thickness greatly influenced the $D_{O_2}$ measurements ($-38$ to $+21\%$ difference). With the use of the root-mean-square average of the cusp thickness over a larger averaging region (diameter $600$ $\mu$m), the error in the $D_{O_2}$ measurements was reduced to $<5\%$ difference from the true value. On the basis of these model results, experimental measurements of $D_{O_2}$ should take into account the variations in cusp thickness using the root-mean-square average.

Weind et al. (14) used a simple mean thickness in their $D_{O_2}$ measurements; thus it is likely that much of the variation in the reported $D_{O_2}$ values for porcine cusps was due to cusp thickness variations. Although individual $D_{O_2}$ measurements may be in error (maximum error estimated to be less than $\pm 40\%$), the mean $D_{O_2}$ reported by Weind et al. should be a good estimate of the true $D_{O_2}$ for the aortic valve. Therefore, the
conclusion derived from this study still holds: a microcirculation is needed to satisfy the \( \text{O}_2 \) demands of the thicker regions of the native aortic valve cusps.

The authors thank Kirsten Weind, Derek Boughner, and Mike Thornton for providing the thickness data used in this study.

**DISCLOSURES**

This research was supported by a Heart and Stroke Foundation of Ontario grant (to C. G. Ellis).

**REFERENCES**


