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Assessment of Transmyocardial Perfusion in Alligator Hearts

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Abstract

Background: Techniques for achieving myocardial perfusion directly from the left ventricular chamber are currently under investigation. Although originally based on the anatomy of reptilian hearts, which are rich in transmural channels and reported to have a poorly developed coronary vasculature, the blood flow capacity of a transmyocardial blood supply has not been studied in these hearts. With the ultimate goal of providing insight into the potential for achieving transmyocardial perfusion in human hearts, we studied the relative contribution of transmyocardial and coronary perfusion in alligator hearts.

Methods and Results: After explantation from six American alligators, the left ventricle was instrumented, and coronary arteries were perfused with oxygenated physiological solution. Using microspheres to estimate regional myocardial perfusion in the beating hearts, we show that although the epicardium was well perfused by the coronary arteries (0.20 +/- 0.08 versus 0.07 +/- 0.01 mL [center dot] min sup -1 [center dot] g sup -1 owing to flow from the ventricular chamber), a significant proportion of endocardial perfusion was from the ventricular chamber (0.21 +/- 0.07 mL [center dot] min sup -1 [center dot] g sup -1 from the left ventricle versus 0.13 +/- 0.04 mL [center dot] min sup -1 [center dot] g sup -1 from coronary arteries).

Conclusions: A significant amount of direct transmyocardial perfusion is present in alligator hearts. The conditions that apparently permit this situation in reptilian hearts are reviewed, and their implications for aiding in the optimization of techniques for achieving transmyocardial flow in humans are discussed. (Circulation. 1997;95:1585-1591.)

Key Words: coronary disease, microcirculation, perfusion, microspheres.

Techniques for achieving myocardial perfusion directly from the left ventricular (LV) chamber, such as transmyocardial laser revascularization, are currently under investigation. [1,2] Whether physiologically significant amounts of blood actually flow through these transmyocardial laser revascularization channels in human and experimental animal hearts remains controversial. The idea of transmyocardial revascularization was originally based on the concepts that in reptilian hearts the epicardial coronary circulation is poorly developed and that the myocardium is predominantly oxygenated directly by LV blood percolating through a network of intramyocardial channels and sinusoids. [3,4] However, the physiology of "transmyocardial" flow (ie, blood flow from the ventricle directly into the myocardium) has not been well studied. With the ultimate goal of providing insight into the potential for achieving transmyocardial perfusion in human hearts, we studied the contribution of transmyocardial perfusion relative to that provided by the coronary arteries in alligator hearts.

Methods

The major experiments of this study were performed in hearts from six long-term-captive American alligators (length, 3.0 to 3.6 m; weight, 270 to 340 kg) scheduled for euthanasia. Euthanasia was carried out in the usual manner for alligators (spinal cord transection). Hearts were explanted and immersed in oxygenated physiological solution. Hearts were then connected to the perfusion apparatus shown schematically in Figure 1 In brief, the aortic valve cusps were sutured together to prevent ejection from the LV chamber (required for the protocol as detailed below). The two coronary arteries were separately cannulated with 8F pediatric arterial cannula, and a thin cannula (3- to 4-mm diameter) was inserted into the LV apex to vent the chamber. The heart was then perfused with oxygenated Tyrode's solution (144 mmol/L NaCl, 5 mmol/L KCl, 0.9 mmol/L $MgCl_2$ [center dot] $6H_2O$, 6 mmol/L HEPES, 15 mmol/L glucose, and 1.5 mmol/L $CaCl_2$, at 25 degrees Celsius), and a mean perfusion pressure was maintained at 40 mm Hg, which is a physiological pressure for alligators. [5,6] A

large-bore cannula (28F) connected to a reservoir was inserted into the LV chamber through the left atrial appendage, which was held in place by an umbilical ligature. At the completion of this surgical preparation, the coronary circulation was completely separated from perfusion derived directly from within the LV chamber. A microtip pressure transducer (Millar) was introduced into the cannula to measure the LV pressure. The total flow rate of the perfusate to the heart was measured by an in-line flow probe (Transonics). The heart was paced at 30 bpm.

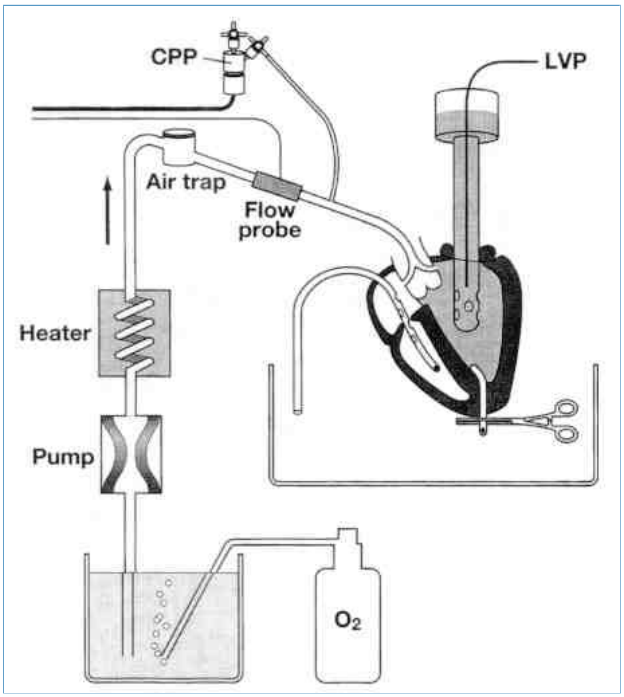

Figure 1. Alligator Langendorff heart preparation in which coronary flow could be separated from flow through naturally occurring transmyocardial channels. See text for details. LVP indicates left ventricular pressure.

Colored microspheres (6 x 10^5 spheres/0.2 mL, 15- micro meter diameter; Triton Technology) were injected into the perfusion line [nearly equal] 25 cm from the heart to measure the contribution of the coronary arteries to regional myocardial perfusion. Then, the LV was volume loaded with oxygenated Tyrode's solution to achieve a peak LV systolic pressure of 40 mm Hg (again, a physiological pressure for alligators). After stabilization, 0.5 mL mixed microsphere solution (of a different color than that injected into the coronary arteries) was injected every 2 minutes into the LV for a total of 6 minutes (total of 1.5 mL or 4.5 x 10^6 spheres injected) to assess the contribution of blood flow from the ventricle to the myocardium. At the end of each 2-minute period, a 1-mL sample of LV perfusate was obtained (for determination of microsphere concentration), and the LV was quickly drained through the apical vent. The LV was then refilled with the same amount of perfusate, and the next injection was performed. At the end of the study, [nearly equal] 1-g myocardial samples were taken from both the spongy endocardial myocardium and the more densely packed epicardial myocardium of the LV. The microspheres were retrieved from these samples (by myocardial digestion), and their numbers were analyzed in the standard manner. [7]

Regional perfusion from the coronary circulation (RP_{CC}) was calculated in the standard manner for direct coronary injection of microspheres [8]: Equation 1 where CF_{total} is the total coronary perfusion flow measured from the in-line flow probe, N is the number of microspheres detected in the sample per 1 g tissue, and N_{total} is the total number of microspheres injected into the coronary perfusion line.

$$RP_{CC} = CF_{total} \times N/N_{total}$$

Equation 1

Regional perfusion due to "transmyocardial" blood flow from the LV chamber (RP_{TM}) was assessed by the following equation: Equation 2 where N is the number of spheres per 1 g tissue in the sample, N_{LV} is the number of spheres per 1 mL perfusate sampled from within the LV chamber, and T is the duration of exposure of the LV to the microspheres, which in our case was always 6 minutes. For the case that the flow pattern is of a to-and-fro nature between the LV chamber and the myocardium, this equation may underestimate the magnitude of myocardial perfusion due to blood flow directly from the ventricular chamber (see the "Discussion").

$$RP_{TM} = N/(N_{LV} \times T)$$

Equation 2

Samples removed for histological analysis were fixed overnight in 10% neutral buffered formalin before dehydration and paraffin embedding. Sections (4 micro meter) were stained with hematoxylin and eosin and trichrome stains. Myocardial samples were examined with standard light microscopy (x250) with a calibrated micrometer for quantification of endomyocardial sheet widths (rationale described in detail below).

Five additional hearts were used to obtain casts of the vasculature. Casts of the coronary arteries were made by cannulating right and left coronary arteries and manually injecting 20 mL casting medium mixed with the catalyst and promoter (Batson's No. 17 Plastic Replica and Corrosion Kit, Polysciences, Inc) as described previously. [9] Red casting material was injected into the right coronary artery, and blue casting material was injected into the left coronary artery. In two hearts of small alligators (1.5 m long), casts were made by injecting the material into the LV chamber through a cannula placed through the mitral valve (no coronary injection) after the aorta was ligated at the annulus, thus blocking the coronary ostia. After the casting material injections were completed, the hearts were kept in water for at least 3 hours to complete the polymerization. The myocardium was then corroded with a maceration solution at 50 degrees Celsius and rinsed in water several times up to 24 hours, and the casts were recovered.

In three other hearts, black tissue dye (Bradley Products) was infused either into the coronary arteries (n = 1) or directly into the ventricular chamber (n = 2) to delineate the regions of myocardium perfused from the respective source. The two coronary arteries were individually flushed with 10% buffered formaldehyde, and the ventricular chamber was also flushed through a cannula placed through the mitral valve. The coronary injection was performed after fixation, at which time the left coronary artery was cannulated and 10 mL dye was injected to allow observation of the epicardial coronary arteries and the distribution of their perfusion throughout the myocardium. For ventricular injections, hearts of the small alligators were used. The heart was prepared fresh as detailed above for casting material injection; in addition, the proximal coronary arteries were severed near the aorta so that no inadvertent flow of dye could reach the myocardium through these vessels. Dye was then infused into the chamber and allowed to percolate for [nearly equal] 15 to 30 minutes. The heart was then fixed in formalin and cut for photography and microscopy. For intraventricular injection of both dye and casting material, injections were performed with a pressure head of 25 to 35 mm Hg achieved by manual compression of a syringe connected to a cannula within the chamber.

Statistical Analysis

Coronary flow rates and flow rates directly from the chamber calculated from microsphere analysis were expressed as mean + /- SEM. Coronary and direct myocardial flow rates were compared with a paired t test, with a value of $P < .05$ considered statistically significant.

Results

Anatomy and Histological Appearance of the Alligator Heart

Alligator hearts have two aortas: a small left aorta arising from the right ventricle and a larger right aorta coming from the left ventricle. Both aortic valves are bicuspid. There are two prominent coronary arteries arising from the right aorta that frequently share a common ostium originating on the right ventricular side of the aorta. Macroscopically, the myocardium exhibits two zones (Figure 2(A)). On the endocardial side is a thick ([nearly equal] 1.5 cm), spongy-appearing endocardial zone with prominent channels extending deep into the myocardial wall. On the epicardial side is a thin (2 to 3 mm) layer of densely packed myocardium. Black dye injected into the coronary arteries revealed an extensive, well-developed epicardial network (Figure 2(B)) that stains the entire myocardium, including the endocardial region (Figure 2(C)). A coronary cast is shown in Figure 2 (D); the right coronary artery is shown in red, and the left coronary artery is shown in blue. This cast confirms the existence of a fine, extensive, small vessel network richly supplying the myocardium.

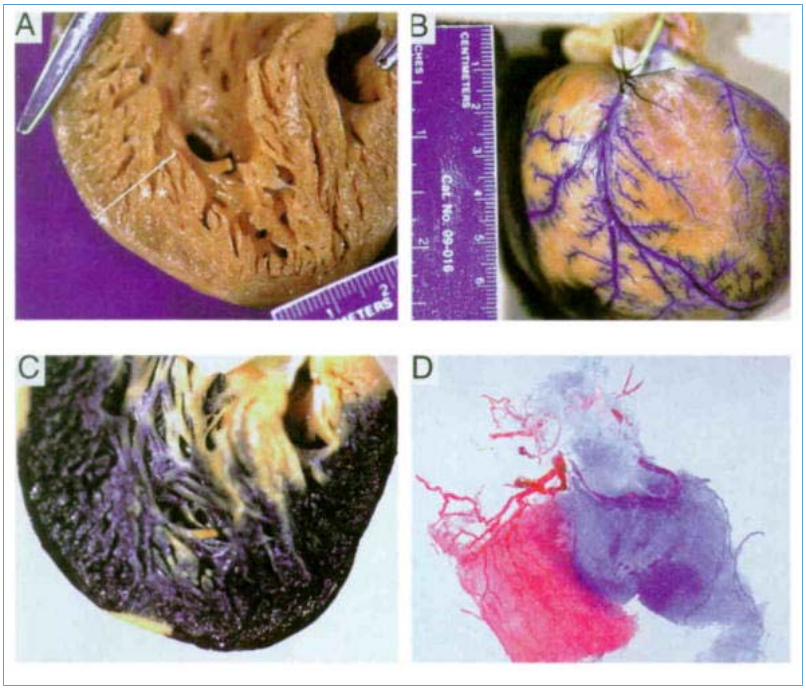

Figure 2. A, Gross view of transected alligator heart demonstrating the spongy endocardium (**) and the more densely packed and thin epicardium (*). B, Intracoronary black dye injection reveals a well-developed epicardial coronary artery system. C, Transected view of heart after intracoronary black dye injection shows that coronary artery system perfuses the entire wall of the ventricle, including the spongy endocardial layer all the way to the endocardium. D, Coronary cast showing the extensive vascular network throughout the myocardium (right coronary artery in red; left coronary artery in blue).

When dye was injected into the ventricular chamber (no dye through the coronary ostia), there was faint patchy staining of the epicardial zone and dense staining in the entire endocardial zone (Figure 3(A)). Neither the right ventricular side of the septum nor the right ventricular free wall was stained. On the epicardial surface, faint myocardial staining was evident before the heart was sectioned, and importantly, some dye had reached the epicardial artery, indicating the existence of connections between the ventricular chamber and the epicardial circulation (Figure 3(B)). Accordingly, it is not surprising that microscopic examination of samples taken from these hearts revealed dye within the epicardial sinusoids and small vessels of the endocardial zone (Figure 4(A)) and, to a lesser degree, within vessels in the epicardial zone (Figure 4(B)). Figure 3(C) shows an anterior-posterior view of a cast made of the left ventricle. A thin sheet of very small vessels (blue arrows), which appears to represent a shallow zone of vascular communication between the ventricular chamber and the epicardial zone, has been removed over the anterior surface to reveal the larger endocardial zone channels (white arrow). The casting material did not reach all the way through the epicardial zone or into epicardial vessels. The large endocardial channels are better visualized in the lateral view of the cast in which the thin layer of fluffy vessels has been removed (Figure 3(D)).

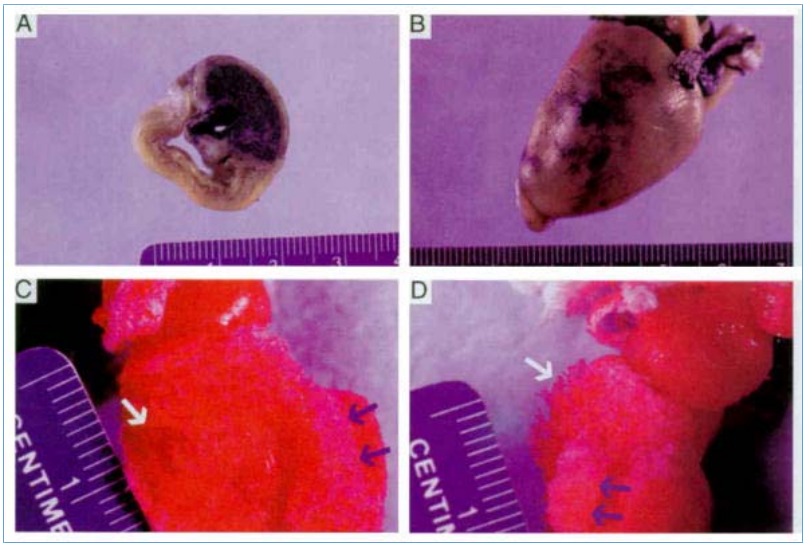

Figure 3. A, Cross section of the heart of a 1.5-m-long alligator in which black dye was placed in the ventricular chamber after the coronary ostia were blocked. Dense pigmentation of endocardial zone is evident, but there is only faint, spotty staining of the epicardial zone, indicating relatively inefficient vascular connections to the

epicardial zone from ventricular source. B, Epicardium of a heart in which dye was injected into the ventricular chamber; some dye does appear in epicardial myocardium, and importantly, some dye appears in the epicardial artery, indicating the existence of communication between endocardial sinusoids and epicardial circulation. C, Anterior-posterior view of a cast made from within the left ventricle. A thin fluffy sheet of very small vessels (blue arrows), which appears to represent a shallow zone of vascular communication between the ventricular chamber and the epicardial zone, has been removed over the anterior surface to reveal the larger endocardial zone channels (white arrow). D, Lateral view of the same cast more clearly shows the large arborizing endocardial channels (white arrow) in the region where the thinner vessels have been removed.

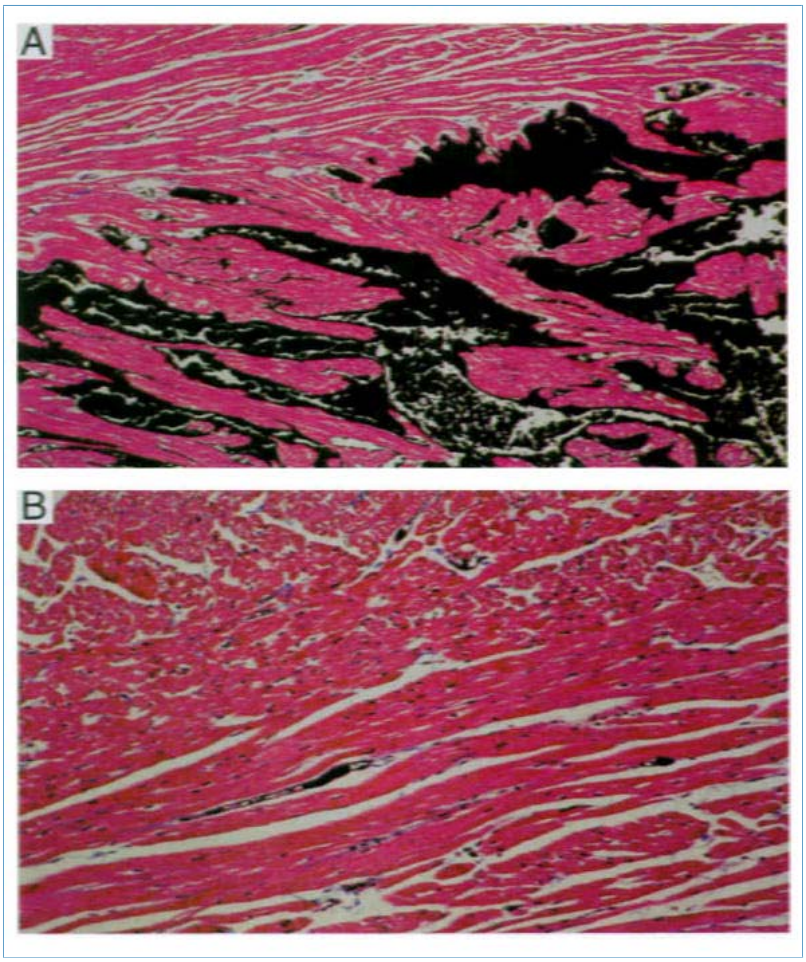

Figure 4. Trichrome-stained histological sections (A, x40; B, x200) of alligator heart in which black dye was injected only into the left ventricular chamber after the coronary ostia were blocked. A, The border between the endocardial and epicardial zones where dense staining is seen within the large sinusoid, within vascular structures in the myocardial sheets, and clearly within vessels at the base of the myocardial sheets. B, The appearance of black dye is seen within vessels of the epicardial zone.

The endocardial and epicardial zones are clearly visible on a cross-sectional histological sample (Figure 5 (A)). The abundant, large-caliber channels emanating from the LV chamber and extending into the wall and creating thin "sheets" of myocardium are readily appreciated at low magnification (Figure 5(B)). The relatively loose myocyte packing of the endocardium caused by the extensive channels surrounding groups of myocytes is further appreciated at a higher magnification (Figure 5(C)). The resulting sheets of myocytes range between two and eight cells thick, ranging from [nearly equal] 60 to 450 micro meter and averaging 194 +/- 86 micro meter (mean +/- SD). The significant microvasculature is also seen in these sections (note the nucleated sickle-shaped red blood cells in the vessels); these structures may represent venules or sinusoids that connect to the ventricular chamber. Because the channel density is so high, the distance from the ventricular chamber to the center of myocyte sheets (which represents the diffusion distance for nutrients) averaged 97 +/- 45 micro meter (range, 30 to 225 micro meter as determined from the analysis of 100 endocardial-myocardial sheets from samples taken from six alligator hearts).

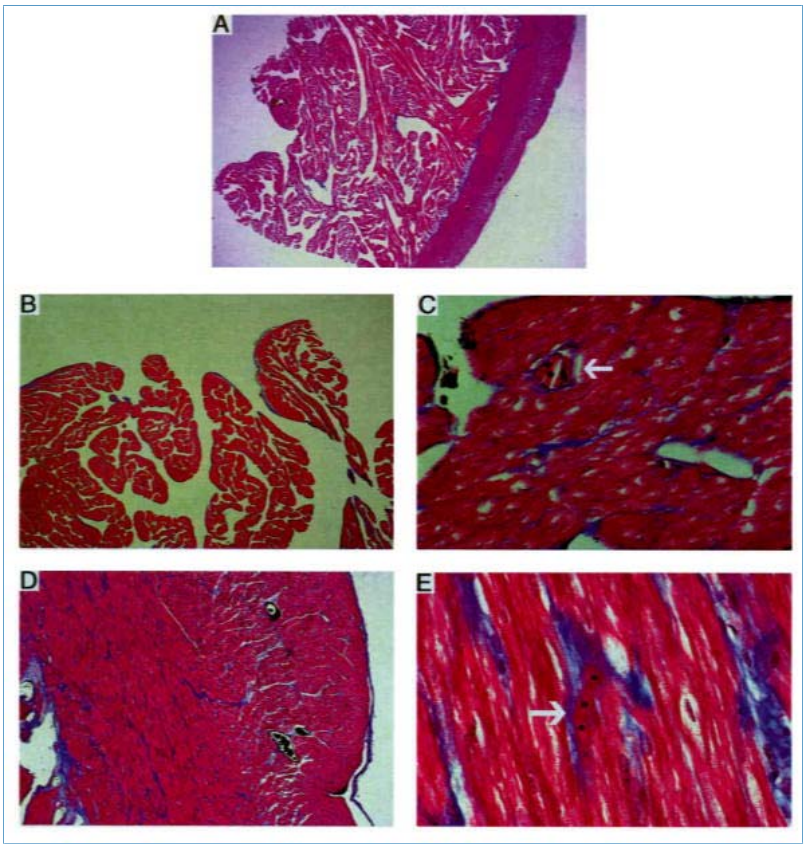

Figure 5. Trichrome-stained histological section (A, x1.5) spanning the entire left ventricular wall showing the spongy endocardium with extensive channels and sinusoids and the more densely packed epicardial region. The extensiveness of the channels is further appreciated in magnified views of the endocardial zone (B, x25). Higher magnifications (C, x400) reveal that even deep inside the endocardial zone, the myocardium contains many capillaries (note the nucleated red blood cells [arrows]). The densely packed epicardial zone appears similar to mammalian myocardium even at higher magnifications (D, x25; E, x400), except for nucleated red blood cells.

It is also readily appreciated that the high channel density results in a very high surface area for the interface between the chamber and the myocytes. In contrast, the epicardial zone is more densely packed, lacks the large channels and sinusoids, and bears a striking resemblance to mammalian muscle (Figure 5(D and E)).

Relative Contributions of Coronary and Transmyocardial Perfusion

(Figure 6) shows representative spectra obtained from the epicardial and endocardial zones of an isolated alligator heart. In this example, white spheres were injected into the coronary arteries, and yellow spheres were injected into the LV chamber. In the epicardial zone, the prominent white peak and lack of significant contribution of yellow microspheres indicated that this region was perfused mainly by the coronary arteries and that there was less of a contribution due to blood flow directly from the ventricular chamber. In contrast, the sample from the endocardial zone had prominent white and yellow peaks, indicating contributions from both modes of perfusion. Table 1 summarizes the mean (+/- SEM) results of the quantitative analysis of spectra obtained from six hearts (total of 16 endocardial samples and 16 epicardial samples). In the epicardial layer, estimated coronary perfusion accounted for [nearly equal] 70% of total flow, whereas [nearly equal] 30% was derived from the chamber. The situation was reversed for the endocardial side, where > 60% of the perfusion was derived directly from the ventricular chamber. As noted in "Methods" and as will be reviewed further, these estimates of direct blood flow from the ventricular chamber are lower limits because of the possible to-and-fro nature of the perfusion.

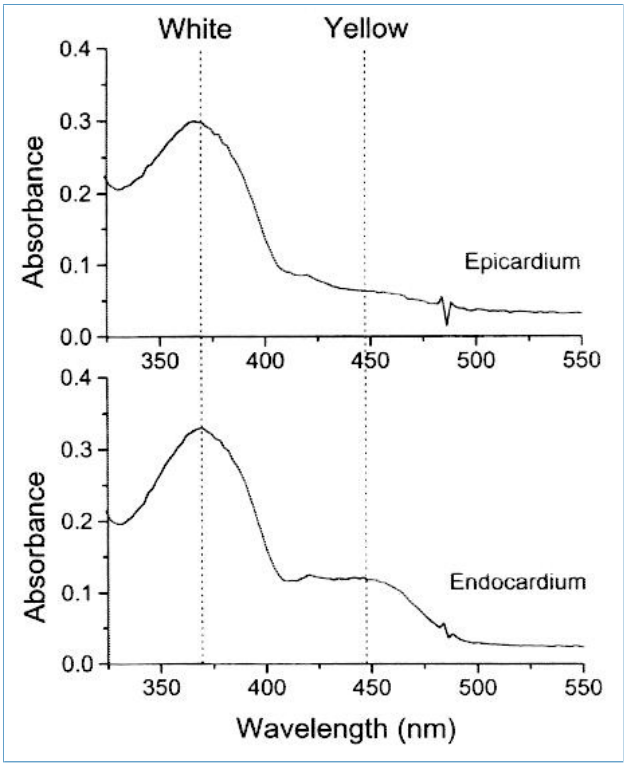

Figure 6. Representative spectra from myocardium in which white spheres were injected into coronaries and yellow spheres were injected into the left ventricular cavity. Spectrum from the epicardial layer (top) shows a prominent peak caused by coronary flow but only a small contribution of flow directly from the left ventricular chamber. In contrast, although endocardium (bottom) still has significant perfusion from coronaries, there is a large contribution of perfusion directly from the chamber. See text for further details related to quantification of flow from the spectral peak amplitudes.

Region	Coronary Flow, mL · min^{-1} · g^{-1}	Transmyocardial Flow,* mL · min^{-1} · g^{-1}
Epicardium	0.20±0.08	0.07±0.01‡
Endocardium	0.13±0.04	0.21±0.07†

Values given are mean±SEM (n=6 hearts, a total of 16 samples).
*Numbers reflect lower limits of transmyocardial flow. See text for further details.
†P<.05 vs coronary flow by paired t test.
‡P=.10 vs coronary flow by paired t test.

Table 1. Estimated Contributions of Coronary-Derived Flow and Direct Transmyocardial Flow From the Ventricular Chamber by Region

Discussion

It has been assumed for a long time that hearts of reptiles have a more poorly developed coronary vasculature than do hearts of mammals and that they derive direct myocardial perfusion from within the ventricle. However, details of this physiology have not been investigated previously. In the present study, we show that alligator hearts, including those of 300-kg alligators whose hearts are roughly the size of hearts from 20-kg dogs, have two morphologically distinct zones: a relatively thin epicardial zone of densely packed myocytes similar in appearance to mammalian myocardium and a thicker endocardial zone composed of more loosely packed myocardium whose sponge-like appearance derives from the extensive network of sinusoids and large channels that emanate from the LV chamber and richly innervate the myocardium. Contrary to expectations, there is also an extensive, well-developed epicardial coronary arterial network that links to a microcirculation that extends through the entire myocardial wall to the subendocardium. Microsphere-derived estimates of regional myocardial perfusion corresponded well with expectations based on regional anatomy. The epicardial zone received substantial perfusion from the coronary arteries, with a small contribution of direct blood flow from the ventricular chamber. The endocardial zone had a dual supply that derived in large part from perfusion directly from the ventricular chamber under the conditions of our experiments. Although of a significantly smaller magnitude, there was significant coronary artery-derived flow in the endocardial zone.

Efforts to achieve transmyocardial revascularization in cardiac patients, and mammals in general, appear to have been initially fueled in part by the assumption that such a mechanism contributes importantly to reptilian myocardial perfusion. [3,4,10] To the best of our knowledge, this is the first study to directly test and confirm that this is the case. Better understanding of the factors that permit this large degree of direct perfusion from the ventricular chamber to occur in reptile hearts may help us understand and optimize techniques of achieving direct myocardial perfusion from the ventricular chamber through channels made in mammalian hearts. Several features revealed in the present study are pertinent in this regard. First, on an anatomic basis, the channels leading from the chamber into the myocardium are very large (visible by eye) and connect to an extensive, high-density, branching network of smaller channels. The resulting sheets of myocardium averaged only [nearly equal] 190 micro meter thick. Thus, the dense channel network creates a very high surface area for nutrient exchange, with the myocytes in the deepest portions of the sheets averaging only 95 micro meter from the surface. Accordingly, we can infer that this anatomy results in the ability of intraventricular blood to oxygenate a large mass of myocytes within the endocardial zone. Finally, to accommodate both a very high channel density and a sufficient mass of myocytes, the endocardial zone is very thick (greater or equal to 1.5 cm compared with the 2- to 3-mm thickness of the epicardial zone).

Physiological factors (not investigated in the present study) may also contribute to the ability to achieve large amounts of direct myocardial perfusion from the ventricular chamber. Alligators at rest have low body metabolic rates and consequently require little perfusion at rest. Indeed, it is remarkable that an [nearly equal] 150-g heart can support an alligator weighing > 300 kg. Under resting conditions, heart rate, mean blood pressure, and diastolic blood pressure are very low compared with those of mammals. [5,6,11] These factors lead to low myocardial wall stress, which is likely to be a major determinant of the dynamics of fluid exchange between the chamber and the channels. With these factors in mind, it is pertinent to question whether direct myocardial perfusion from the ventricular chamber in alligators occurs during systole or diastole, an issue that remains unresolved. This point could not be addressed in the present study.

The histological appearance of acute and chronic artificial channels made with lasers in the experimental setting [10,12-16] and in those obtained from a limited number of human autopsy specimens [17-19] differ significantly from those of alligator hearts. No histological sample has ever shown the high density of channels with significant amounts of myocardium in close proximity (ie, within reasonable oxygen diffusion distances) to the channels seen in the alligator hearts. The channels are generally smaller and lack the extensive ramifications into smaller channels, although there is some evidence from human autopsy specimens, [17-19] rat hearts, [20] and dog hearts [12] that suggests that over time vascular structures may emanate from the original channel. Also, significant differences exist in physiological factors (heart rate, arterial and ventricular pressures, myocardial wall stress, etc), the contributions of which need to be considered.

These findings also validate previous microsphere studies of transmyocardial blood flow in dog hearts in which channels were made with various lasers and flow was calculated as either low or negligible. [12,21,22] Because methods for calculating flow with microspheres were developed and validated in conventional circulatory systems in which perfusion is unidirectional from arterioles through capillary beds, [7,8] it has been argued that these techniques are not applicable to detect direct myocardial perfusion from the chamber where the flow pathways might resemble percolation more that perfusion. In view of this theoretical concern, therefore, it is important that the present study using microsphere techniques demonstrates significant flow in alligator hearts. On the other hand, it remains likely that to-and-fro flow could wash microspheres out of sinusoids and trabeculations and back into the pool of LV blood. To the extent that this occurs, the quantification of flow in alligator hearts should be viewed as a lower limit that might underestimate the actual contribution of direct myocardial perfusion from the ventricular chamber. Finally, the finding that dye and casting material injected directly into the ventricular chamber appeared in both endocardial and epicardial zones indicates that direct ventricular myocardial connections exist and have the capacity to carry fluid. This suggests that the myocardium can be perfused, not merely superfused, as would be the case with to-and-fro blood flow exchange between the chamber and the channels surrounding the sheets of myocardium in the endocardial zone.

In summary, we have demonstrated a high degree of direct myocardial perfusion from the ventricular chamber in the endocardial region of alligator hearts. The anatomic features associated with this finding are a very high density of channels and thin sheets of myocardium that permit both a high surface area for nutrient exchange and (in principle) reasonable diffusion distances between a large mass of myocytes and the ventricular chamber. The large wall thickness allows for a large mass of myocytes to be contained within the endocardial zone rich in transmyocardial blood supply. Many fundamental questions remain about the physiology of alligator myocardial perfusion that are not addressed in this initial study. Nevertheless, the information obtained thus far represents a significant step that may provide important reference points for many aspects of the quest to achieve transmyocardial blood flow in patients.

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IMAGE GALLERY

Select All **Export Selected to PowerPoint**

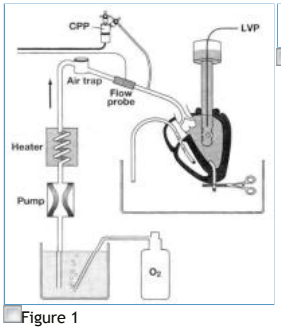


Figure 1

$$RP_{CC} = CF_{total} \times N/N_{total}$$

Equation 1

$$RP_{TM} = N/(N_{LV} \times T)$$

Equation 2

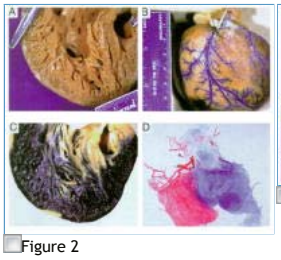


Figure 2

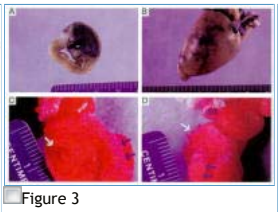
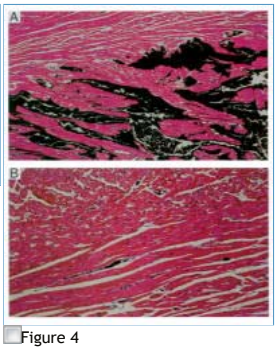


Figure 3



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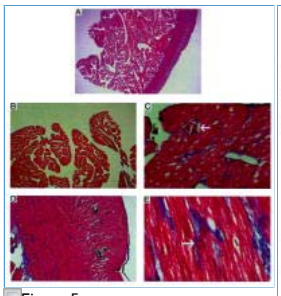

Figure 5

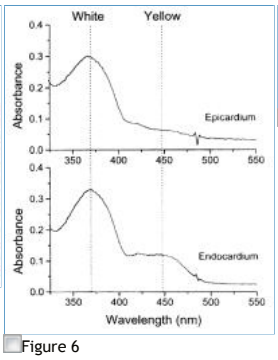

Figure 6

Region	Coronary Flow, mL · min⁻¹ · g⁻¹	Transmyocardial Flow,* mL · min⁻¹ · g⁻¹
Epicardium	0.20 ± 0.08	0.07 ± 0.01‡
Endocardium	0.13 ± 0.04	0.21 ± 0.07†

Values given are mean ± SEM (n = 6 hearts, a total of 16 samples).
*Numbers reflect lower limits of transmyocardial flow. See text for further details.
†P < .05 vs coronary flow by paired *t* test.
‡P = .10 vs coronary flow by paired *t* test.

Table 1

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