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Review

Myocardial water handling and the role of aquaporins

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Abstract

Cardiac surgery is performed in approximately 770,000 adults and 30,000 children in the United States of America annually. In this review we outline the mechanistic links between post-operative myocardial stunning and the development of myocardial edema. These interrelated processes cause a decline in myocardial performance that account for significant morbidity and mortality after cardiac surgery. Factors leading to myocardial edema include hemodilution, ischemia and reperfusion as well as osmotic gradients arising from pathological change. Several members of the aquaporin family of water transport proteins have been described in the myocardium although their role in the pathogenesis and resolution of cardiac edema is not established. This review examines evidence for the involvement of aquaporins in myocardial water handling during normal and pathological conditions.

Keywords: Membrane permeability; Myocardium; Cardiopulmonary bypass; Myocardial edema; Aquaporin; Dystrophin associated complex

Contents

1. Introduction

Interest in this area has been stimulated by the clinical observation that cardiac performance is predictably diminished after cardiac surgery. This phenomenon is known as myocardial stunning and is largely responsible for low cardiac output syndrome. The resulting hypo-perfusion of important organs including kidney and brain accounts for the majority of morbidity in current adult and pediatric cardiac surgical practice.

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Myocardial stunning is associated with cell swelling, altered mitochondrial morphology and function [1,2]. It is well recognized clinically, with a decline in cardiac performance seen 2–12 h following cardiac surgery [3]. The development of myocardial edema during this period is not well reported but does occur [4]. It is the primary cause of acute diastolic dysfunction, or impaired ability of the heart to relax during diastole, necessitating higher filling pressures to generate satisfactory cardiac output [5].

Most cardiac operations involve the use of cardiopulmonary bypass (the 'heart–lung machine') which pumps oxygenated blood to the body whilst the heart and lungs are isolated. The conduct of cardiopulmonary bypass involves hemodilution, and an inflammatory process is established as the blood flows across the foreign surfaces of the extracorporeal circuit. These factors combine to promote whole body water accumulation, much of it in the interstitial space [6,7]. In addition, the heart suffers the metabolic effects of ischemia and reperfusion. The generation of intracellular lactate creates a strong inwardly directed osmotic gradient that causes cardiomyocytes to swell and may impair ventricular performance contributing to the clinical syndrome of stunning [8].

In this review, we examine water transport in the normal heart and how this may vary in pathological circumstances. We pay particular attention to the potential role of trans-cellular water movement mediated by aquaporins (AQPs) and an overview of this group of proteins is provided in Section I.

2. Section I—Aquaporins

AQP proteins form transmembrane channels which facilitate movement of water molecules along osmotic gradients. There are 13 AQPs, found in mammals (AQP0–12), most of which permit transcellular passage of water while some also allow passage of glycerol (AQP3, 7, 9 and 10). In some circumstances, heavy metal salts, chloride, CO2 and ammonia may also be transported by aquaporins. Most AQPs display organ- and cell-specific expression which sometimes differs between species. Highly specific regional expression of different AQPs combine to coordinate water movement in a number of organs. For instance AQP1 expression in the proximal tubule of the kidney facilitates the initial extraction of water to concentrate urine. This process is an example of near-isosmolar water movement driven by active solute transport. Later, in the principal cells of the collecting duct AQP2 is sequestered within vesicles which, in response to vasopressin receptor activation, insert into the apical membrane to facilitate water reabsorption into the tubular cell. Expression of AQP3 and 4 in the basolateral membrane then allows the water to move into the hypertonic interstitium of the medulla and finally to return to the circulation.

Much of our understanding of AQP function comes from analysis of pathological situations. Within the brain, AQP4 is integral to the blood brain barrier and is primarily responsible for the development of cerebral edema following cytotoxic injury [9]. Thus, AQP4 knockout mice demonstrate significant survival benefits compared to wild type mice following stroke and, traumatic brain injury, with benefits also seen in meningitis and water intoxication [9–12]. Conversely, AQP4 knockout mice suffer poorer outcome in models of vasogenic edema as this water channel facilitates removal of water from the brain [13]. AQP4 is anchored to the blood vessel-encapsulating astrocytic foot processes through a protein complex involving syntrophin and dystrophin. In skeletal muscle where the role of AQP4 is less well defined it is similarly associated with the dystrophin protein complex. In the skeletal muscle disease Duchene muscular dystrophy (DMD), AQP4 protein is reduced in association with absent dystrophin protein, although this does not appear to primarily contribute to the muscle weakness [14].

Information on mammalian AQP structure is based on analysis of AQP1. Monomers consist of 6 transmembrane helices which form "hourglass" pores. In the cell membrane monomers combine to form a tetrameric complex, although each monomer is independently functional. Due to the design of the channel, requiring reorientation of water molecules during transit, the pore is highly specific to water and excludes H^+ passage [15]. Water moves rapidly through AQPs, and the increase in permeability attributable to AQP4 is significantly greater than that caused by AQP1 [16,17]. Gating of mammalian water channels does not appear to be a consistent feature in studies thus far, however pH and phosphorylation influenced permeability in some cases e.g. pulmonary AQP3 permeability was reduced by low pH [18] and *Xenopus* oocytes containing AQP4 had reduced permeability when phosphorylated [19]. Overall, AQP function is largely subject to transcriptional, rather than short term regulation by pH or other influences [20].

AQP1 is the ubiquitous water channel found in endothelial cell membranes of vascular tissues throughout the body. It is also found in the plasma membranes of the red blood cell, kidney, lung, brain and eye [15]. It was the first AQP discovered after being demonstrated in erythrocytes and shown to permit rapid water permeability in response to an osmotic gradient [21,22]. The study of AQP1 null individuals, arising as a result of mutation in the AQP1 gene leading to little or no AQP1 expression has provided an insight into the function of AQP1 in humans. In these subjects, the permeability of pulmonary endothelium was studied by computerized tomography following a 3 l intravenous volume load. Pulmonary venules of AQP1 null humans were engorged, compared to control subjects that showed imminent interstitial pulmonary edema in the form of peribronchiolar edema, the thickness of the airway walls increasing by 40–50% [23]. It is likely that this is due to a decrease in pulmonary vascular permeability, as the study of AQP1 knockout mice, under different conditions, has not revealed defects in alveolar or pleural reabsorption, with no impairment in lung fluid or gas transport physiology [24,25].

3. Section II—Myocardial water handling

Accumulation of excess interstitial fluid in the normal heart is prevented by anatomical and physiological factors. As blood traverses the myocardial capillary bed, it may leave via either the coronary sinus, emptying into the right atrium, or via thebesian veins that drain directly into the ventricular cavities. As

the majority of fluid flux occurs in the post-capillary venules, easy passage or 'run off' is important. Any fluid that accumulates in the interstitium is handled by myocardial lymphatics which return water to the circulation via the thoracic duct.

The balance of microvascular fluid filtration is modeled by the Starling forces, reviewed in detail by Melhorn et al. in the context of myocardial fluid dynamics [4]. Many of the factors driving water movement are affected during cardiac surgery including the plasma colloid osmotic pressure, which is reduced by hemodilution, and the compressive force of regular myocardial contractions, which cease when the heart is arrested in diastole for the performance of the operation. These factors combine to produce altered fluid filtration and a shift in the balance towards accumulation of water in the interstitium.

When describing myocardial water permeability, most authors are actually describing the net effect of water movement between the vascular compartment and the interstitium. This is partly determined by exposure of the interstitium to blood vessels, essentially capillary density or surface area available for water flux, which is very high in the heart compared to other organs. Furthermore, the pore size determining permeability of these microvessels is thought to be very high, combining to produce a 'leaky' endothelium compared to microvessels in other organs [4]. Many investigators consider basal filtration rate through the capillary to equal interstitial clearance of water through lymph channels. It is not known how the cardiac microcirculation compensates for chronic abnormalities of lymph flow as exist following cardiac transplantation, where connections to the thoracic duct are severed, and in patients who have undergone total cavo-pulmonary connections where elevated upper body venous pressures may diminish lymph flow through the thoracic duct.

Broadly speaking water traverses the cell membrane by one of 3 main routes: (i) by diffusion through the lipid bi-layer, (ii) coupled to ion-channels or substrate transporters, such as glucose, Na^+, K^+, Ca^{++} and (iii) via AQPs, which selectively permit rapid movement of water in response to osmotic gradients [26]. Water moves across the lipid bi-layer bidirectionally in response to osmotic gradients as a result of shifts in ionic and substrate concentrations. With regard to water movement across the endothelium of the myocardium, Kellen and Bassingthwaighte highlight the functional significance of the inter-endothelial clefts as well as the aquaporins [27]. They demonstrate that inter-endothelial cell clefts account for two thirds of water movement across the capillary bed and into the interstitial space, with a third passing through AQP water channels [28].

Water movement between the interstitium and intracellular space has been relatively ignored compared to factors regulating microvascular permeability. This may be because in normal circumstances, cardiomyocytes are not subject to variations in the extracellular osmotic environment. Intracellular water represents approximately 77% of total tissue water [29] and maintenance of interstitial and cardiomyocyte volumes are inextricably linked through osmotically obliged water movement. This may be clinically important in circumstances where (i) interstitial fluid volumes are increased because of pathologically increased microvascular permeability, such as cardiopulmonary bypass or sepsis, and (ii) when there is an inwardly directed osmotic gradient as a result of cellular events such as ischemia where accumulation of lactate osmotically draws water into the cell during reperfusion [30].

The potential role of AQPs in the development of cardiac edema has been explored in a number of species with differing conclusions. The techniques used include video-microscopic observation of osmotically induced changes in cell volume and assessment of sarcolemmal water permeability by measuring the rate of swelling or shrinkage. Together with an assessment of the Arrhenius activation energy (*E*a), which is a measure of the energy barrier to water flux (normally high because diffusion of water is limited by the lipid bi-layer) the contribution of AQPs to net sarcolemmal water permeability can be estimated. On the basis of these measurements, Ogura et al. showed that AQPs represent a major route of water transport in guinea pig and rat heart cells [31,32]. The inhibitory effect of adding Hg^{2+} (a non-specific AQP inhibitor) on interstitial fluid volumes further confirmed these findings. Similar techniques were used by Suleymanian and Baumgarten [33] in rabbit ventricular cardiomyocytes. They demonstrated similar sarcolemmal permeability but a higher *E*a and concluded that diffusion, not water channels, were the predominant path of water movement in the rabbit. Species differences in AQP expression may explain this discrepancy and the contribution of AQPs to human cardiomyocyte water movement is, at present, unknown. Osmotic regulation of cell volume affects a number of other sarcolemmal processes including K^+ channel activity with significant implications for cardiac electrical activity [34] and susceptibility to arrhythmias [26].

In the unusual circumstance where there is an outwardly directed osmotic gradient, as occurs during sepsis and after cardiopulmonary bypass, endothelial AQPs are proposed to be primarily responsible for the movement of water out of the expanded interstitial space and into the capillary [28]. In several non-cardiac tissues, such as brain [9,11,12] and cornea [35] the involvement of AQPs in the development and resolution of tissue edema has been demonstrated by comparative phenotype studies using knockout mice. This provides a rational basis for postulating a role of AQPs in cardiac edema.

4. Section III—Myocardial edema and stunning

Myocardial edema is often considered a secondary phenomenon and a downstream effect of the primary pathological process such as myocardial ischemia, allograft rejection or systemic inflammatory process. In fact, myocardial edema causes organ dysfunction that may persist long after the original insult and may be more clinically relevant than the treated primary process.

Very small increases in myocardial fluid content are associated with significant systolic ventricular dysfunction [36–46]. In one analysis, a 2.6% gain in myocardial water produced by hypo-osmotic priming solutions for cardiopulmonary bypass was associated with a 43% decline in left ventricular performance and similar order reduction in compliance [43]. A second study demonstrated a 30–50% decline in cardiac output for a given preload when myocardial water content was increased by 3.5% [47]. Diastolic function is also compromised in association with myocardial edema [30,42,46,48–50]. This is particularly relevant in the pediatric setting following cardiac surgery,

as many infants already have impaired diastolic function as a result of hypertrophy related to pre-existing structural lesions.

Myocardial edema also results from ischemia and reperfusion injury [30,50,51]. In several species and models, cellular edema is evident if the ischemic injury lasts more than 15 min [8,30,50,51]. Swelling of organelles and in particular mitochondria is an early event and accounts for the majority of cell swelling. Mitochondria play a central role in myocardial stunning. They are involved in preconditioning, liberation of reactive oxygen species and potentially cell death. Initial movement of water into mitochondria is thought to be part of the early protective response to ischemia, countering the effect of matrix shrinkage that increases the inter-membrane space and is deleterious to respiration [52]. In this context, water is thought to move in response to an influx of K^+ ions, as a result of mitoK_{ATP} channel opening. Chemical openers of this channel, such as diazoxide, have a cardioprotective effect however the pore-forming proteins underlying this protective effect have yet to be identified [53].

After reperfusion, swelling of cardiac mitochondria occurs due to increased permeability of the inner mitochondrial membrane and is probably driven by the osmotic effect of accumulation of anionic proteins, monovalent cations, intermediates of the Krebs cycle and other small organic molecules [54]. This occurs even with the major ion channels closed, and is reversible with long periods of reperfusion [55]. Again, the route by which water travels in this setting is unknown. Excessive swelling may occur with opening of the mitochondrial permeability transition pore (mPTP) which allows non-selective movement of small molecules. This leads to irreversible loss of the mitochondrial membrane potential, uncoupling of the respiratory chain and release of cytochrome C, initiating apoptotic or necrotic cell death [2].

In the kidney the inner mitochondrial membrane contains AQPs, possibly AQP8, that allows excessive swelling without mPTP opening [56]. Chemical inhibitors of AQPs prevented mitochondrial swelling, disruption and cell death. Thus inwardly directed water movement in mitochondria may be beneficial early, then deleterious in subsequent stages of the mitochondrial response to ischemia and reperfusion. Hepatic [57,58] and renal [56] expression of mitochondrial AQPs has been reported, however the functional significance of these findings has not been determined and attempts at localisation frustrated by poor antibody specificity.

When the heart is subject to ischemia, cell swelling is of the cytotoxic type, in response to accumulation of intracellular lactate. Where ischemia is 'planned', as during cardiac surgery involving cardiopulmonary bypass, there are other factors involved and there will also be an element of vasogenic edema arising as a result of the 'capillary leak syndrome'. This syndrome is well described following cardiac surgery, particularly in neonates and infants undergoing corrective surgery for congenital heart disease. It has been described as an 'endotheliopathy' and attributed to an increase in vessel permeability, induced by a systemic inflammatory process initiated by exposure of the blood to foreign surfaces of the cardiopulmonary bypass circuit [59]. Excess capillary filtration and reduced lymphatic clearance (as occurs when the heart is chemically arrested [44]) may promote myocardial edema, and exaggerate the effect of ischemia by increasing the distance between coronary arterial supply and cardiomyocyte [4]. Accordingly, an edematous myocardium is associated with a greater energy requirement to meet the demands of a less efficient contractile apparatus [60].

The increase in total body water and tissue edema is coincident with a predictable decline in cardiac output, leading many to speculate that edema and poor cardiac output are causally related [6,61,62]. In an acute study, the association between edema and cardiac dysfunction is well demonstrated by randomized treatment of infants following cardiopulmonary bypass with modified ultrafiltration (MUF) which reduces plasma volume. Those undergoing MUF suffered less edema, measured as myocardial wall thickness, and demonstrated improved contractility compared to controls [63]. In adults, capillary leak accounts for a 2–5% gain in extracellular fluid volume peaking at 4 h post-cardiopulmonary bypass [6], again corresponding to the peak of myocardial dysfunction [64,65].

The clinical importance of cardiac edema is highlighted by the need to leave the child's sternum open after complex neonatal and infant cardiac procedures [66–68] often requiring prolonged cardiopulmonary bypass. This is done to optimize cardiac performance by reducing sternal compression. After the systemic inflammatory response abates, interstitial fluid clears and myocardial function improves, and the sternum may be closed on the second or third postoperative day. Novel treatments that reduce capillary leak or speed resolution of interstitial edema would provide major clinical benefit.

5. Section IV—Aquaporins and the heart

The myocardial expression of AQPs is poorly characterized. Soon after the initial description of AQP1, it was noted that the cardiac microvasculature and the endocardium express this protein [69]. The abundance of AQP1 protein in cardiac tissue was thought to reflect the dense vascular supply of this organ however early reports suggested that water channels did not play a major role in microvascular filtration in the heart [33] (discussed in Section II). In normal circumstances, cardiomyocytes do not experience osmotic imbalance and to date, cardiac AQPs have not been investigated with the same level of attention that renal and brain AQPs have received.

A contemporary view of myocardial AQP expression would include cells on both sides of the interstitial space, namely the endothelial barrier as well as the sarcolemma of the cardiomyocyte. Evidence of a functional role for AQP1 expression in endothelial cells has been described in Section II [27,28,32]. Myocellular expression has been noted in rat cardiomyocytes [70] with functional interactions demonstrated with caveolae in response to changes in the osmotic environment. We have demonstrated AQP1 expression within t-tubules [71], themselves invaginations of the sarcolemma extending into the myocardium within the Z line structures (see Fig. 1). Ionic fluxes, particularly relevant to Ca^{2+} homeostasis related to electromechanical coupling and K^+ in attenuating the cardiac action potential, may require accompanying rapid osmotic equilibration.

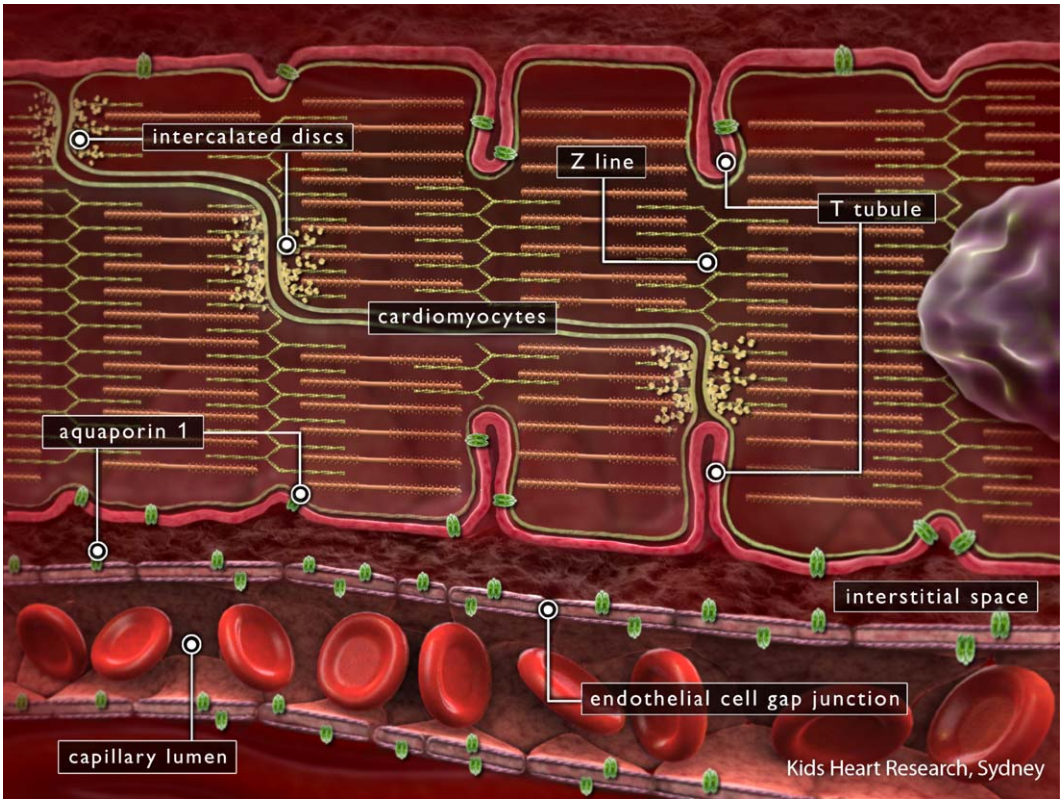

Fig. 1. Expression of AQP1 in the heart. AQP1 is principally distributed in vascular endothelium. AQP1 is also present in membranes associated with the cardiomyocyte, including the sarcolemma and associated invaginations, the t-tubules. Not shown in this depiction is AQP1 expression by red blood cells.

Links between K^+ and water transport are evident in glial cells, with the possibility that such interactions may also be relevant in the heart. AQP4 has been shown to co-localise with the Kir4.1 potassium channel in astrocyte endfeet [72] and this interaction involves the dystrophin-associated proteins (DAP) [73]. Loss of DAP integrity reduces AQP4 expression and the clearance of extracellular potassium leading to seizures [17,74]. In the eye, co-localisation of Kir4.1, AQP4 and DAP have also been demonstrated [75] and reduced expression of AQP4 and Kir4.1 channels may contribute to proliferative retinopathy following disruption to the retinal blood supply [76]. Thus a link may exist between rapid K^+ transport and water permeability at the sarcolemma which impacts upon ionic balance and tolerance of ischaemia. AQP4, Kir4.1 potassium channels and the DAP complex are all present in the mouse heart although the role of cardiac aquaporins in these processes have yet to be established.

Two reports describe myocardial AQP1 expression in disease models. Jonker et al. demonstrated up-regulation of myocardial AQP1 mRNA and protein expression in a model of chronic fetal hypo-osmotic stress caused by hemodilution [77]. Immunohistochemistry showed AQP1 mostly within the vasculature and comparatively little within cardiomyocytes. It is not known whether the observed increase in AQP1 expression acts to increase interstitial edema or facilitates clearance through movement of water back through endothelial cells into the vascular compartment. The second study of AQP1 in a model of clinical practice focused on the effect of cardiopulmonary bypass in the lamb [78]. In this study lambs underwent cardiopulmonary bypass and deep hypothermic circulatory arrest with 6 h of reperfusion following which AQP1 mRNA levels were unchanged. Deficiencies of this study include the small number of animals in each group and utilization of operative techniques now not commonly employed which may produce relatively less inflammatory burden. AQP1 mRNA abundance was not correlated with protein expression. It remains unclear what effect cardiopulmonary bypass might have on expression of AQP1 and how this would affect myocardial edema.

A number of AQPs in addition to AQP1 have been identified in myocardial tissue. Those reported in human, sheep, rat and mouse, searchable through the National Library of Medicine are included in Table 1. Most reports have focused on the identification of relevant mRNA by PCR without correlation with protein expression or site of expression. While many AQP mRNAs are present in the heart, protein is detectable for only a small few and AQP1 expression is both the most prominent and functional in membrane permeability assays [79].

There are limited published data on human myocardial AQP expression, other than AQP1. AQP3 transcript has been identified by RT-PCR [79] and previously by microarray, but without positive staining by immunohistochemistry as shown for other tissues in the study [80]. Absence of AQP3 in myocardium has also been reported based on Northern analysis [81]. AQP4 mRNA has been identified by Northern analysis [82]. This finding was confirmed more recently by RT-PCR, but further analysis revealed a lack of corresponding protein expression [79]. AQP4 is of particular interest due to the noted

Table 1
Myocardial aquaporin expression

	Human	Sheep	Rat	Mouse
AQP0				
AQP1	*present* RT-PCR, IHC, Western-endothelial & myocellular distribution [71,79] Northern [96]	*present* RNAse Protection Assay [78] Northern, Western, IHC-endothelial and minimal myocellular distribution [77]	*present* IHC-endothelial & myocellular distribution [70] RT-PCR, IHC, Western-endothelial & myocellular distribution [71,79] Western, Northern & autoradiography -endothelial [69] Northern [96] RNAse Protection Assay [97] IHC-endothelial [98]	*present* Western [99] RT-PCR, Western, IHC [79]
AQP2	*absent* Microarray and IHC [80] RT-PCR [79]		*absent* RNAse Protection Assay [97] RT-PCR [79]	*absent* Northern [100] RT-PCR [79]
AQP3	*equivocal* present Microarray and IHC [80] RT-PCR [79] absent Northern [81] Western [79]		*equivocal* present RT-PCR, *see ref.* [79] absent Northern [101,102] RNAse Protection Assay [97] Western [79]	*absent* RT-PCR, Western [79]
AQP4	*equivocal* present Northern [82] RT-PCR [79] absent Western [79]		*equivocal* present RT-PCR [79] absent RNAse Protection Assay [97] Western [79]	*present* Northern [103] RT-PCR, Western [79]
AQP5	*equivocal* present RT-PCR [79] *absent* Western [79]		*equivocal* present RT-PCR, *see ref.* [79] absent RNAse Protection Assay [97,104]	*absent* Northern [105] RT-PCR, Western [79]
AQP6	*absent* Northern [106] RT-PCR [79]		*present* RT-PCR [79]	*present* RT-PCR [79]
AQP7	*present* Northern [85,86] RT-PCR [79]		*present* Northern [85,107] RT-PCR [79]	*present* RT-PCR, Western [99] RT-PCR [79]
AQP8	*absent* Northern [89] RT-PCR [79]		equivocal *present* Western [58] *absent* Northern [87,88] RT-PCR [79]	*present* Northern [108] RT-PCR [79]
AQP9	*equivocal* present RT-PCR [79] absent Northern [109]		*present* RT-PCR [79]	*absent* RT-PCR [79]

Table 1 (*continued*)

AQP10	*equivocal* present RT-PCR [79] absent RNAse Protection Assay [110] Northern [111]	N/A (pseudogene)	absent Northern [112]
AQP11	*present* RT-PCR [79]	*present* RT-PCR [79]	*present* Northern [113] RT-PCR [79]
AQP12			*absent* RNA dot blot [114]

loss of AQP4 expression in muscular dystrophies associated with the loss of dystrophin [83] and the cardiomyopathy occurring with such diseases [84]. Human cardiac AQP7 mRNA expression has been identified [79,85,86] and may be derived from cardiac-associated adipose tissue where AQP7 is well described, although it has been demonstrated in rat-derived isolated cardiomyocytes [79]. Screens of human myocardial tissue by PCR using degenerate primers based on the NPA motif common to many AQPs failed to demonstrate any novel AQPs in the heart [71] although low levels of expression may limit the usefulness of this strategy. More recently an RT-PCR screen of human myocardium using available primer sequences additionally demonstrated mRNA for AQP5, 9, 10 and 11 [79].

Numerous AQPs have been found in the hearts of other species (Table 1). AQP8 is reported within the mitochondrial fraction of rat heart by Western blot [58] although is reportedly absent in this species by RT-PCR [79] and Northern analysis [87,88]. AQP8 transcript is readily detectable by RT-PCR in the mouse heart [79]. Comparison of the permeability of heart-derived membranes of wild-type and AQP8 knockout mice suggest that, even if present, this protein is not functionally relevant in the heart [79]. However, if AQP8 was confirmed as being both myocardial and mitochondrial in location, it may be of relevance to the study of ischemia, reperfusion and the response of the cardiomyocyte to this injury. To date, AQP8 has not been identified in human heart [89].

Finally, AQP1 may transport CO_2 as well as water and this may be beneficial to the heart during metabolic stress [90–92]. AQP1 expression in *Xenopus* oocytes increases CO_2 permeability by 40% over controls and this increase is inhibited by blocking AQP1 function with $Hg2^+$ [91]. However physiologically relevant CO_2 transport via aquaporins could not be demonstrated during both normal and stressed states in erythrocytes, lung and kidney cells utilizing relevant knockout mouse materials, despite water permeability being altered by more than 100 fold [24,92–95]. Thus physiologically important CO_2 transport by aquaporins within the heart seems unlikely, but has not been directly studied.

6. Conclusion

Myocardial water handling likely involves AQP1 but the importance of water movement mediated by this and other AQP channels has yet to be defined in health and disease. The conduct of cardiac surgery, particularly in children, involves a series of potent stimuli for water retention. Myocardial edema is a critical element of myocardial stunning and is responsible for significant patient morbidity and mortality. Further characterization of AQPs in the heart will enhance our understanding of the processes involved and may provide opportunities for therapeutic intervention.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbamem.2006.05.021.

References

[1] R. Bolli, E. Marban, Molecular and cellular mechanisms of myocardial stunning, Physiol. Rev. 79 (1999) 609–634.
[2] M. Akao, B. O'Rourke, Y. Teshima, J. Seharaseyon, E. Marban, Mechanistically distinct steps in the mitochondrial death pathway triggered by oxidative stress in cardiac myocytes, Circ. Res. 92 (2003) 186–194.
[3] T.M. Hoffman, G. Wernovsky, A.M. Atz, T.J. Kulik, D.P. Nelson, A.C. Chang, J.M. Bailey, A. Akbary, J.F. Kocsis, R. Kaczmarek, T.L. Spray, D.L. Wessel, Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease, Circulation 107 (2003) 996–1002.
[4] U. Mehlhorn, J. Geissler, A. Laine, S.J. Allen, Myocardial fluid balance, Eur. J. Cardio-thorac. Surg. 20 (2001) 1220–1230.
[5] R.R. Chaturvedi, C. Lincoln, J.W. Gothard, M.H. Scallan, P.A. White, A. N. Redington, D.F. Shore, Left ventricular dysfunction after open repair of simple congenital heart defects in infants and children: quantitation with the use of a conductance catheter immediately after bypass, J. Thorac. Cardiovasc. Surg. 115 (1998) 77–83.

[6] Y. Hamada, K. Kawachi, N. Tsunooka, Y. Nakamura, S. Takano, H. Imagawa, Capillary leakage in cardiac surgery with cardiopulmonary bypass, Asian Cardiovasc. Thorac. Ann. 12 (2004) 193–197.
[7] M.C. Seghaye, R.G. Grabitz, J. Duchateau, S. Busse, S. Dabritz, D. Koch, G. Alzen, H. Hornchen, B.J. Messmer, G. Von Bernuth, Inflammatory reaction and capillary leak syndrome related to cardiopulmonary bypass in neonates undergoing cardiac operations, J. Thorac. Cardiovasc. Surg. 112 (1996) 687–697.
[8] R.A. Kloner, R.B. Jennings, Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 1, Circulation 104 (2001) 2981–2989.
[9] G.T. Manley, M. Fujimura, T. Ma, N. Noshita, F. Filiz, A.W. Bollen, P. Chan, A.S. Verkman, Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke, Nat. Med. 6 (2000) 159–163.
[10] P. Agre, Aquaporin water channels (Nobel Lecture), Angew. Chem., Int. Ed. Engl. 43 (2004) 4278–4290.
[11] G.T. Manley, D.K. Binder, M.C. Papadopoulos, A.S. Verkman, New insights into water transport and edema in the central nervous system from phenotype analysis of aquaporin-4 null mice, Neuroscience 129 (2004) 983–991.
[12] M.C. Papadopoulos, A.S. Verkman, Aquaporin-4 gene disruption in mice reduces brain swelling and mortality in pneumococcal meningitis, J. Biol. Chem. 280 (2005) 13906–13912.
[13] M.C. Papadopoulos, G.T. Manley, S. Krishna, A.S. Verkman, Aquaporin-4 facilitates reabsorption of excess fluid in vasogenic brain edema, FASEB J. 18 (2004) 1291–1293.
[14] A.S. Verkman, Physiological importance of aquaporins: lessons from knockout mice, Curr. Opin. Nephrol. Hypertens. 9 (2000) 517–522.
[15] L.S. King, D. Kozono, P. Agre, From structure to disease: the evolving tale of aquaporin biology, Nat. Rev., Mol. Cell Biol. 5 (2004) 687–698.
[16] D. Kozono, M. Yasui, L.S. King, P. Agre, Aquaporin water channels: atomic structure and molecular dynamics meet clinical medicine, J. Clin. Invest. 109 (2002) 1395–1399.
[17] M. Amiry-Moghaddam, O.P. Ottersen, The molecular basis of water transport in the brain, Nat. Rev., Neurosci. 4 (2003) 991–1001.
[18] M. Zelenina, A.A. Bondar, S. Zelenin, A. Aperia, Nickel and extracellular acidification inhibit the water permeability of human aquaporin-3 in lung epithelial cells, J. Biol. Chem. 278 (2003) 30037–30043.
[19] Z. Han, M.B. Wax, R.V. Patil, Regulation of aquaporin-4 water channels by phorbol ester-dependent protein phosphorylation, J. Biol. Chem. 273 (1998) 6001–6004.
[20] A.S. Verkman, More than just water channels: unexpected cellular roles of aquaporins, J. Cell Sci. 118 (2005) 3225–3232.
[21] G.M. Preston, P. Agre, Isolation of the cDNA for erythrocyte integral membrane protein of 28 kilodaltons: member of an ancient channel family, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 11110–11114.
[22] G.M. Preston, T.P. Carroll, W.B. Guggino, P. Agre, Appearance of water channels in *Xenopus* oocytes expressing red cell CHIP28 protein, Science 256 (1992) 385–387.
[23] L.S. King, S. Nielsen, P. Agre, R.H. Brown, Decreased pulmonary vascular permeability in aquaporin-1-null humans, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 1059–1063.
[24] A.S. Verkman, Aquaporin water channels and endothelial cell function, J. Anat. 200 (2002) 617–627.
[25] Y. Song, T. Ma, M.A. Matthay, A.S. Verkman, Role of aquaporin-4 in airspace-to-capillary water permeability in intact mouse lung measured by a novel gravimetric method, J. Gen. Physiol. 115 (2000) 17–27.
[26] A.R. Wright, S.A. Rees, Cardiac cell volume: crystal clear or murky waters? A comparison with other cell types, Pharmacol. Ther. 80 (1998) 89–121.
[27] M.R. Kellen, J.B. Bassingthwaighte, An integrative model of coupled water and solute exchange in the heart, Am. J. Physiol.: Heart Circ. Physiol. 285 (2003) H1303–H1316.
[28] M.R. Kellen, J.B. Bassingthwaighte, Transient transcapillary exchange of water driven by osmotic forces in the heart, Am. J. Physiol.: Heart Circ. Physiol. 285 (2003) H1317–H1331.
[29] P.I. Polimeni, J. Al-Sadir, Expansion of extracellular space in the nonischemic zone of the infarcted heart and concomitant changes in tissue electrolyte contents in the rat, Circ. Res. 37 (1975) 725–732.
[30] D. Garcia-Dorado, J. Oliveras, Myocardial oedema: a preventable cause of reperfusion injury? Cardiovasc. Res. 27 (1993) 1555–1563.
[31] T. Ogura, S. Imanishi, T. Shibamoto, Osmometric and water-transporting properties of guinea pig cardiac myocytes, Jpn. J. Physiol. 52 (2002) 333–342.
[32] T. Ogura, H. Matsuda, S. Imanishi, T. Shibamoto, Sarcolemmal hydraulic conductivity of guinea-pig and rat ventricular myocytes, Cardiovasc. Res. 54 (2002) 590–600.
[33] M.A. Suleymanian, C.M. Baumgarten, Osmotic gradient-induced water permeation across the sarcolemma of rabbit ventricular myocytes, J. Gen. Physiol. 107 (1996) 503–514.
[34] T. Ogura, H. Matsuda, T. Shibamoto, S. Imanishi, Osmosensitive properties of rapid and slow delayed rectifier K+ currents in guinea-pig heart cells, Clin. Exp. Pharmacol. Physiol. 30 (2003) 616–622.
[35] A.S. Verkman, Novel roles of aquaporins revealed by phenotype analysis of knockout mice, Rev. Physiol. Biochem. Pharmacol. 155 (2005) 31–55.
[36] J. Albers, A. Schroeder, R. de Simone, R. Mockel, C.F. Vahl, S. Hagl, 3D evaluation of myocardial edema: experimental study on 22 pigs using magnetic resonance and tissue analysis, Thorac. Cardiovasc. Surg. 49 (2001) 199–203.
[37] R. Goto, H. Tearle, D.J. Steward, P.G. Ashmore, Myocardial oedema and ventricular function after cardioplegia with added mannitol, Can. J. Anaesth. 38 (1991) 7–14.
[38] Z.C. Weng, A.C. Nicolosi, P.W. Detwiler, D.T. Hsu, S.W. Schierman, A.H. Goldstein, H.M. Spotnitz, Effects of crystalloid, blood, and University of Wisconsin perfusates on weight, water content, and left ventricular compliance in an edema-prone, isolated porcine heart model, J. Thorac. Cardiovasc. Surg. 103 (1992) 504–513.
[39] R.E. Carlson, A.M. Aisen, A.J. Buda, Effect of reduction in myocardial edema on myocardial blood flow and ventricular function after coronary reperfusion, Am. J. Physiol. 262 (1992) H641–H648.
[40] C.E. Cross, P.A. Rieben, P.F. Salisbury, Influence of coronary perfusion and myocardial edema on pressure–volume diagram of left ventricle, Am. J. Physiol. 201 (1961) 102–108.
[41] J.R. Utley, G.B. Michalsky, L.R. Bryant, K. Mobin-Uddin, H.E. McKean, Determinants of myocardial water content during cardiopulmonary bypass, J. Thorac. Cardiovasc. Surg. 68 (1974) 8–16.
[42] H.J. Geissler, S.J. Allen, Myocardial fluid balance: pathophysiology and clinical implications, Thorac. Cardiovasc. Surg. 46 (Suppl. 2) (1998) 242–245 (discussion 246–7).
[43] R.P. Foglia, H.L. Lazar, D.L. Steed, D.M. Follette, A.J. Manganaro, E. Deland, G.D. Buckberg, Iatrogenic myocardial edema with crystalloid primes: effects on left ventricular compliance, performance, and perfusion, Surg. Forum 29 (1978) 312–315.
[44] S.J. Allen, H.J. Geissler, K.L. Davis, G.R. Gogola, R.D. Warters, E.R. de Vivie, U. Mehlhorn, Augmenting cardiac contractility hastens myocardial edema resolution after cardiopulmonary bypass and cardioplegic arrest, Anesth. Analg. 85 (1997) 987–992.
[45] H.M. Spotnitz, Effects of edema on systolic and diastolic function in vivo, J. Cardiothorac. Surg. 10 (1995) 454–459.
[46] C.X. Jia, D.G. Rabkin, J.P. Hart, D.A. Dean, S.A. Cabreriza, A.D. Weinberg, H.M. Spotnitz, Regional variation in myocardial water content in the edematous pig heart, J. Surg. Res. 106 (2002) 70–75.
[47] G.A. Laine, S.J. Allen, Left ventricular myocardial edema. Lymph flow, interstitial fibrosis, and cardiac function, Circ. Res. 68 (1991) 1713–1721.
[48] G. Pogatsa, E. Dubecz, G. Gabor, The role of myocardial edema in the left ventricular diastolic stiffness, Basic Res. Cardiol. 71 (1976) 263–269.
[49] C. Mavroudis, P.A. Ebert, Hemodilution causes decreased compliance in puppies, Circulation 58 (1978) I155–I159.
[50] H.M. Spotnitz, D.T. Hsu, Myocardial edema: importance in the study of left ventricular function, Adv. Card. Surg. 5 (1994) 1–25.
[51] B.S. Palmer, M. Hadziahmetovic, T. Veci, M.G. Angelos, Global ischemic duration and reperfusion function in the isolated perfused rat heart, Resuscitation 62 (2004) 97–106.
[52] P. Dos Santos, A.J. Kowaltowski, M.N. Laclau, S. Seetharaman, P. Paucek, S. Boudina, J.B. Thambo, L. Tariosse, K.D. Garlid, Mechanisms by which

opening the mitochondrial ATP- sensitive K(+) channel protects the ischemic heart, Am. J. Physiol. : Heart Circ. Physiol. 283 (2002) H284–H295.
[53] B. O'Rourke, Evidence for mitochondrial K+ channels and their role in cardioprotection, Circ. Res. 94 (2004) 420–432.
[54] A.D. Beavis, R.D. Brannan, K.D. Garlid, Swelling and contraction of the mitochondrial matrix. I. A structural interpretation of the relationship between light scattering and matrix volume, J. Biol. Chem. 260 (1985) 13424–13433.
[55] F. Bosetti, A. Baracca, G. Lenaz, G. Solaini, Increased state 4 mitochondrial respiration and swelling in early post-ischemic reperfusion of rat heart, FEBS Lett. 563 (2004) 161–164.
[56] W.K. Lee, U. Bork, F. Gholamrezaei, F. Thevenod, Cd2+-induced cytochrome *c* release in apoptotic proximal tubule cells: role of mitochondrial permeability transition pore and Ca2+ uniporter, Am. J. Physiology.: Renal Physiol. 288 (2005) F27–F39.
[57] D. Ferri, A. Mazzone, G.E. Liquori, G. Cassano, M. Svelto, G. Calamita, Ontogeny, distribution, and possible functional implications of an unusual aquaporin, AQP8, in mouse liver, Hepatology 38 (2003) 947–957.
[58] G. Calamita, D. Ferri, P. Gena, G.E. Liquori, A. Cavalier, D. Thomas, M. Svelto, The inner mitochondrial membrane has aquaporin-8 water channels and is highly permeable to water, J. Biol. Chem. 280 (2005) 17149–17153.
[59] L.H. Edmunds Jr., Inflammatory response to cardiopulmonary bypass, Ann. Thorac. Surg. 66 (1998) S12–S16 (discussion S25–28).
[60] H. Kahles, V.A. Mezger, G. Hellige, P.G. Spieckermann, H.J. Bretschneider, The influence of myocardial edema formation on the energy consumption of the heart during aerobiosis and hypoxia, Basic Res. Cardiol. 77 (1982) 158–169.
[61] G. Wernovsky, D. Wypij, R.A. Jonas, J.E. Mayer, F.L. Jr., P.R. Hanley, A.Z. Hickey, A.C. Walsh, A.R. Chang, J.W. Castaneda, et al., Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest, Circulation 92 (1995) 2226–2235.
[62] T. Maehara, I. Novak, R.K. Wyse, M.J. Elliot, Perioperative monitoring of total body water by bio-electrical impedance in children undergoing open heart surgery, Eur. J. Cardiothorac. Surg. 5 (1991) 258–264 (discussion 265).
[63] M.J. Davies, K. Nguyen, J.W. Gaynor, M.J. Elliott, Modified ultrafiltration improves left ventricular systolic function in infants after cardiopulmonary bypass, J. Thorac. Cardiovasc. Surg. 115 (1998) 361–370.
[64] W.M. Breisblatt, K.L. Stein, C.J. Wolfe, W.P. Follansbee, J. Capozzi, J.M. Armitage, R.L. Hardesty, Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery, J. Am. Coll. Cardiol. 15 (1990) 1261–1269.
[65] D.T. Mangano, Biventricular function after myocardial revascularization in humans: deterioration and recovery patterns during the first 24 h, Anesthesiology 62 (1985) 571–577.
[66] S. Tabbutt, B.W. Duncan, D. McLaughlin, D.L. Wessel, R.A. Jonas, P.C. Laussen, Delayed sternal closure after cardiac operations in a pediatric population, J. Thorac. Cardiovasc. Surg. 113 (1997) 886–893.
[67] R.S. Iyer, J.P. Jacobs, M.R. de Leval, J. Stark, M.J. Elliott, Outcomes after delayed sternal closure in pediatric heart operations: a 10-year experience, Ann. Thorac. Surg. 63 (1997) 489–491.
[68] J.N. Odim, C.I. Tchervenkov, A.R. Dobell, Delayed sternal closure: a lifesaving maneuver after early operation for complex congenital heart disease in the neonate, J. Thorac. Cardiovasc. Surg. 98 (1989) 413–416.
[69] C. Bondy, E. Chin, B.L. Smith, G.M. Preston, P. Agre, Developmental gene expression and tissue distribution of the CHIP28 water-channel protein, Proc. Natl. Acad. Sci. U S A 90 (1993) 4500–4504.
[70] E. Page, J. Winterfield, G. Goings, A. Bastawrous, J. Upshaw-Earley, D. Doyle, Water channel proteins in rat cardiac myocyte caveolae: osmolarity-dependent reversible internalization, Am. J. Physiol. 274 (1998) H1988–H2000.
[71] C.G. Au, S.T. Cooper, H.P. Lo, A.G. Compton, N. Yang, E.M. Wintour, K.N. North, D.S. Winlaw, Expression of aquaporin 1 in human cardiac and skeletal muscle, J. Mol. Cell. Cardiol. 36 (2004) 655–662.
[72] E.A. Nagelhus, T.M. Mathiisen, O.P. Ottersen, Aquaporin-4 in the central nervous system: cellular and subcellular distribution and coexpression with KIR4.1, Neuroscience 129 (2004) 905–913.
[73] E. Guadagno, H. Moukhles, Laminin-induced aggregation of the inwardly rectifying potassium channel, Kir4.1, and the water-permeable channel, AQP4, via a dystroglycan-containing complex in astrocytes, Glia 47 (2004) 138–149.
[74] F.E. Dudek, M.A. Rogawski, Regulation of brain water: is there a role for aquaporins in epilepsy? Epilepsy Curr. 5 (2005) 104–106.
[75] N.C. Connors, P. Kofuji, Potassium channel Kir4.1 macromolecular complex in retinal glial cells, Glia 53 (2006) 124–131.
[76] S. Tenckhoff, M. Hollborn, L. Kohen, S. Wolf, P. Wiedemann, A. Bringmann, Diversity of aquaporin mRNA expressed by rat and human retinas, NeuroReport 16 (2005) 53–56.
[77] S.S. Jonker, L.E. Davis, J.D.W. van der Bilt, B. Hadder, A.R. Hohimer, G.D. Giraud, K.L. Thornburg, Anaemia stimulates aquaporin 1 expression in the fetal sheep heart, Exp. Physiol. 88 (2003) 691–698.
[78] S. Tabbutt, D.P. Nelson, N. Tsai, T. Miura, P.R. Hickey, J.E. Mayer, E.J. Neufeld, Induction of aquaporin-1 mRNA following cardiopulmonary bypass and reperfusion, Mol. Med. 3 (1997) 600–609.
[79] T.L. Butler, C.G. Au, B. Yang, J.R. Egan, Y.-M. Tan, E.S. Hardeman, K.N. North, A.S. Verkman, D.S. Winlaw, Cardiac aquaporin expression in human, rat and mouse, Am. J. Physiol.: Heart Circ. Physiol. (Mar 31 2006), doi:10.1152/ajpheart.00090.2006.
[80] A. Mobasheri, S. Wray, D. Marples, Distribution of AQP2 and AQP3 water channels in human tissue microarrays, J. Mol. Histol. 36 (2005) 1–14.
[81] K. Ishibashi, S. Sasaki, F. Saito, T. Ikeuchi, F. Marumo, Structure and chromosomal localization of a human water channel (AQP3) gene, Genomics 27 (1995) 352–354.
[82] B. Yang, T. Ma, A.S. Verkman, cDNA cloning, gene organization, and chromosomal localization of a human mercurial insensitive water channel, J. Biol. Chem. 270 (1995) 22907–22913.
[83] A. Frigeri, G.P. Nicchia, R. Balena, B. Nico, M. Svelto, Aquaporins in skeletal muscle: reassessment of the functional role of aquaporin-4, FASEB J. 18 (2004) 905–907.
[84] F. Muntoni, Cardiomyopathy in muscular dystrophies, Curr. Opin. Neurol. 16 (2003) 577–583.
[85] K. Ishibashi, K. Yamauchi, Y. Kageyama, F. Saito-Ohara, T. Ikeuchi, F. Marumo, S. Sasaki, Molecular characterization of human Aquaporin-7 gene and its chromosomal mapping, Biochim. Biophys. Acta 1399 (1998) 62–66.
[86] H. Kuriyama, S. Kawamoto, N. Ishida, I. Ohno, S. Mita, Y. Matsuzawa, K. Matsubara, K. Okubo, Molecular cloning and expression of a novel human aquaporin from adipose tissue with glycerol permeability, Biochem. Biophys. Res. Commun. 241 (1997) 53–58.
[87] Y. Koyama, T. Yamamoto, D. Kondo, H. Funaki, E. Yaoita, K. Kawasaki, N. Sato, K. Hatakeyama, I. Kihara, Molecular cloning of a new aquaporin from rat pancreas and liver, J. Biol. Chem. 272 (1997) 30329–30333.
[88] K. Ishibashi, M. Kuwahara, Y. Kageyama, A. Tohsaka, F. Marumo, S. Sasaki, Cloning and functional expression of a second new aquaporin abundantly expressed in testis, Biochem. Biophys. Res. Commun. 237 (1997) 714–718.
[89] N. Koyama, K. Ishibashi, M. Kuwahara, N. Inase, M. Ichioka, S. Sasaki, F. Marumo, Cloning and functional expression of human aquaporin8 cDNA and analysis of its gene, Genomics 54 (1998) 169–172.
[90] G.J. Cooper, Y. Zhou, P. Bouyer, I.I. Grichtchenko, W.F. Boron, Transport of volatile solutes through AQP1, J. Physiol. 542 (2002) 17–29.
[91] N.L. Nakhoul, B.A. Davis, M.F. Romero, W.F. Boron, Effect of expressing the water channel aquaporin-1 on the CO2 permeability of *Xenopus* oocytes, Am. J. Physiol. 274 (1998) C543–C548.
[92] R.T. Miller, Aquaporin in the heart—Only for water? J. Mol. Cell. Cardiol. 36 (2004) 653–654.
[93] X. Fang, B. Yang, M.A. Matthay, A.S. Verkman, Evidence against aquaporin-1-dependent CO2 permeability in lung and kidney, J. Physiol. 542 (2002) 63–69.
[94] B. Yang, N. Fukuda, A. van Hoek, M.A. Matthay, T. Ma, A.S. Verkman, Carbon dioxide permeability of aquaporin-1 measured in erythrocytes and lung of aquaporin-1 null mice and in reconstituted proteoliposomes, J. Biol. Chem. 275 (2000) 2686–2692.

[95] A.S. Verkman, Does aquaporin-1 pass gas? An opposing view, J. Physiol. 542 (2002) 31.
[96] H. Hasegawa, S.C. Lian, W.E. Finkbeiner, A.S. Verkman, Extrarenal tissue distribution of CHIP28 water channels by in situ hybridization and antibody staining, Am. J. Physiol. 266 (1994) C893–C903.
[97] F. Umenishi, A.S. Verkman, M.A. Gropper, Quantitative analysis of aquaporin mRNA expression in rat tissues by RNase protection assay, DNA Cell Biol. 15 (1996) 475–480.
[98] S. Nielsen, B.L. Smith, E.I. Christensen, P. Agre, Distribution of the aquaporin CHIP in secretory and resorptive epithelia and capillary endothelia, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 7275–7279.
[99] L.N. Nejsum, M. Elkjaer, H. Hager, J. Frokiaer, T.H. Kwon, S. Nielsen, Localization of aquaporin-7 in rat and mouse kidney using RT-PCR, immunoblotting, and immunocytochemistry, Biochem. Biophys. Res. Commun. 277 (2000) 164–170.
[100] B. Yang, T. Ma, Z. Xu, A.S. Verkman, cDNA and genomic cloning of mouse aquaporin-2: functional analysis of an orthologous mutant causing nephrogenic diabetes insipidus, Genomics 57 (1999) 79–83.
[101] M. Echevarria, E.E. Windhager, S.S. Tate, G. Frindt, Cloning and expression of AQP3, a water channel from the medullary collecting duct of rat kidney, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 10997–11001.
[102] K. Ishibashi, S. Sasaki, K. Fushimi, S. Uchida, M. Kuwahara, H. Saito, T. Furukawa, K. Nakajima, Y. Yamaguchi, T. Gojobori, et al., Molecular cloning and expression of a member of the aquaporin family with permeability to glycerol and urea in addition to water expressed at the basolateral membrane of kidney collecting duct cells, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 6269–6273.
[103] T. Ma, B. Yang, A.S. Verkman, Gene structure, cDNA cloning, and expression of a mouse mercurial-insensitive water channel, Genomics 33 (1996) 382–388.
[104] H. Funaki, T. Yamamoto, Y. Koyama, D. Kondo, E. Yaoita, K. Kawasaki, H. Kobayashi, S. Sawaguchi, H. Abe, I. Kihara, Localization and expression of AQP5 in cornea, serous salivary glands, and pulmonary epithelial cells, Am. J. Physiol. 275 (1998) C1151–C1157.
[105] C.M. Krane, J.E. Towne, A.G. Menon, Cloning and characterization of murine Aqp5: evidence for a conserved aquaporin gene cluster, Mamm. Genome 10 (1999) 498–505.
[106] T. Ma, B. Yang, W.L. Kuo, A.S. Verkman, cDNA cloning and gene structure of a novel water channel expressed exclusively in human kidney: evidence for a gene cluster of aquaporins at chromosome locus 12q13, Genomics 35 (1996) 543–550.
[107] K. Ishibashi, M. Kuwahara, Y. Gu, Y. Kageyama, A. Tohsaka, F. Suzuki, F. Marumo, S. Sasaki, Cloning and functional expression of a new water channel abundantly expressed in the testis permeable to water, glycerol, and urea, J. Biol. Chem. 272 (1997) 20782–20786.
[108] T. Ma, B. Yang, A.S. Verkman, Cloning of a novel water and urea-permeable aquaporin from mouse expressed strongly in colon, placenta, liver, and heart, Biochem. Biophys. Res. Commun. 240 (1997) 324–328.
[109] K. Ishibashi, M. Kuwahara, Y. Gu, Y. Tanaka, F. Marumo, S. Sasaki, Cloning and functional expression of a new aquaporin (AQP9) abundantly expressed in the peripheral leukocytes permeable to water and urea, but not to glycerol, Biochem. Biophys. Res. Commun. 244 (1998) 268–274.
[110] S. Hatakeyama, Y. Yoshida, T. Tani, Y. Koyama, K. Nihei, K. Ohshiro, J.I. Kamiie, E. Yaoita, T. Suda, K. Hatakeyama, T. Yamamoto, Cloning of a new aquaporin (AQP10) abundantly expressed in duodenum and jejunum, Biochem. Biophys. Res. Commun. 287 (2001) 814–819.
[111] K. Ishibashi, T. Morinaga, M. Kuwahara, S. Sasaki, M. Imai, Cloning and identification of a new member of water channel (AQP10) as an aquaglyceroporin, Biochim. Biophys. Acta 1576 (2002) 335–340.
[112] T. Morinaga, M. Nakakoshi, A. Hirao, M. Imai, K. Ishibashi, Mouse aquaporin 10 gene (AQP10) is a pseudogene, Biochem. Biophys. Res. Commun. 294 (2002) 630–634.
[113] Y. Morishita, T. Matsuzaki, M. Hara-chikuma, A. Andoo, M. Shimono, A. Matsuki, K. Kobayashi, M. Ikeda, T. Yamamoto, A. Verkman, E. Kusano, S. Ookawara, K. Takata, S. Sasaki, K. Ishibashi, Disruption of aquaporin-11 produces polycystic kidneys following vacuolization of the proximal tubule, Mol. Cell. Biol. 25 (2005) 7770–7779.
[114] T. Itoh, T. Rai, M. Kuwahara, S.B. Ko, S. Uchida, S. Sasaki, K. Ishibashi, Identification of a novel aquaporin, AQP12, expressed in pancreatic acinar cells, Biochem. Biophys. Res. Commun. 330 (2005) 832–838.