EDEMA DOES MATTER

To the Editor:

My colleagues and I read with great interest the recent article by Butler and colleagues titled, "Dysfunction Induced by Ischemia Versus Edema: Does Edema Matter?"¹ The authors demonstrated significant myocyte swelling after exposure to ischemia and hypotonic solutions (0.75 T) and reduced myocyte contractility after exposure to the ischemic solution but not the hypotonic solution. In an isolated rat heart model, they demonstrated a significant reduction in systolic function during exposure to hypotonic solution. The authors conclude that their data argue against edema as a major contributor to reduced cardiac performance.

Data from our laboratory using a different ischemic solution (metabolic inhibition) demonstrate that ischemia does result in isolated myocyte swelling and reduced contractility, similar to the authors' findings. However, when we evaluated changes in isolated myocytes exposed to isolated osmotic challenges, we found a *direct* relationship between volume change and contractility. This relationship was consistent after exposure to both hypotonic and hypertonic solutions.² Hypertonic solutions were associated with improved isolated myocyte contractility. Hypotonic solutions (0.9 T and 0.6 T) were associated with a reduction in myocyte contractility that was clearly related to the amount of myocyte swelling.² This is in contrast

to the authors' findings. We have also confirmed these findings in isolated human myocytes (after exposure to osmotic challenge as well as metabolic inhibition) (unpublished). We have thus proposed that during cardiac surgery, myocyte edema secondary to osmotic challenge (including exposure to commonly used cardioplegic solutions) does detrimentally affect contractility in a manner that is separate from, and additive to, the widely recognized "ischemia-based" edema and reduced contractility.³

Experimental differences between the two articles exist in that the authors used a shorter protocol (8 vs 20 minutes of exposure), different ischemic and hypotonic solutions, and a different species, all of which may make direct comparisons of data difficult. However, the relationship between isolated myocyte swelling and contractility has been consistently and repeatedly demonstrated in our laboratory after exposure to hyperkalemic cardioplegia, osmotic stress, and metabolic inhibition in myocytes obtained from two animal species and humans.

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Reply to the Editor:

We thank Dr Lawton for her interest in our article¹ and the Editor for the

opportunity to respond. Our principal focus is postoperative low cardiac output syndrome (LCOS) in pediatric patients. By studying myocardial water content and function, we were expecting to scientifically validate the clinical dogma linking edema with dysfunction. However, use of three related models—isolated myocytes, Langendorff hearts,¹ and whole animals on cardiopulmonary bypass²—failed to implicate edema as a significant causal influence in LCOS.

We found that cells swelled in response to hypotonic stress (7%) more than they did in response to ischemia (2%). Cell function was not changed during or after swelling alone but severely affected by ischemia (reduced to 51% of baseline). When hypotonic stress followed the ischemic insult, we showed additional edema (from 2% to 6%) but no additional contractile dysfunction. From these findings, we assert that ischemia is the most important influence on contractile function.

We examined a single tonic change (0.75 T)¹ whereas the Lawton group (Mizutani and associates³) used both mild (0.9 T) and severe (0.6 T) hypotonic exposure. Cell shortening was identically reduced after recovery in both the 0.9 T and 0.6 T groups (~30%) and was also reduced in the 1.0 T isotonic control (15%–20%). Much of the impairment is simply temporal decline, also seen in our study by repeated measurement of isotonic controls and a characteristic of the model itself. In the Lawton study, statistical significance could only be shown by comparison of the 0.6 T and 0.9 T groups with a 2.6 T hypertonic group. No significant difference was shown in cell function between 0.6 T, 0.9 T, and isotonic buffers in agreement with our own work.

In the Lawton group's study, degree of swelling correlated well with severity of tonic change, but cell shortening was not affected to the same degree. For cells exposed to 0.6 T buffer, 30% swelling was seen, whereas cells

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exposed to 0.9 T showed a 7% increase in volume. Shortening was reduced by approximately 30% after recovery in both 0.6 T and 0.9 T groups. Thus, despite a 23% difference in size between groups, there was no difference in function.³ This argues against a direct relationship between edema and dysfunction.

In Dr Lawton's study, function was measured only in the recovery phase, when cardiomyocytes had returned to their normal size and not during the time in which cells were swollen. Yet, in the clinical context, edema and dysfunction occur concurrently, and this has largely been the basis for a causal association to be drawn. Data we present from Langendorff-based analyses show only a limited association exists. An increase in water content of 3.3% was associated with a 9% reduction in developed pressure, which in this model is a modest decline. Developed pressure was stable for up to 20 minutes of hypotonic exposure and returned to baseline with isotonic reperfusion.¹ Our surgical modeling suggests that swelling is tolerated for several hours without functional effect. Thus, it is unlikely that the duration of hypotonic exposure, a further methodologic difference between our studies, was responsible for the lack of edema-related dysfunction.

It must be acknowledged that experimental separation of tonicity from ischemia, removing osmotic influences of the interstitial and vascular compartments, is highly artificial. Future use of human myocytes in this model will also be subject to the same caveats. It is likely that the dogma relating edema to dysfunction confuses *extracellular* water accumulation, as a result of capillary leak and renal effects of lower cardiac output, with *intracellular* water accumulation, which is well tolerated by the heart and quickly resolves through transmembrane water exchange.^{4,5}

The most credible interpretation of data from both our groups is that the swollen heart of "myocardial edema"

as observed by surgeons after long neonatal cardiac surgery actually represents the effects of myocardial dysfunction with the ventricles working at a higher intracavitary volume and reduced fractional shortening, almost all of which can be attributed to the effects of ischemia and reperfusion. The water content of the myocardium itself may be increased by a few percentage points, and this contributes to a decrease in cardiac performance by a similar amount.

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WHAT IS THE REAL RISK OF STENT-GRAFT INFECTION IN THE TREATMENT OF AORTOBRONCHIAL FISTULAS?

To the Editor:

A recent article by Hacker and colleagues¹ describes a single case report of aortobronchial fistula (ABF) in a patient who was successfully treated (27 years ago) for isthmus posttraumatic

pseudoaneurysm by placement of thoracic endoprosthesis. The authors conclude by saying that "endovascular intervention and stent grafting are feasible and should be the first option in the treatment of ABFs."

We agree that ABF is a rare and fatal disease and most frequently associated with previous cardiac, vascular, or thoracic surgery. Surgical treatment is still characterized by high rates of mortality and morbidity. Our article² showed that it is not possible to identify a half-accurate diagnostic instrument: angiography, bronchoscopy, and transesophageal echocardiography are associated with a high rate of complications, including fatal hemorrhage. Findings suggestive of ABF on computed tomography scan include pseudoaneurysm, aortic anatomy abnormalities, lung parenchyma consolidation, and compression of bronchial tree.

Conventional open surgical correction involves a thoracotomy and has fairly high morbidity and mortality because of difficult operative dissection associated with reoperative surgery; in addition, patients may have severe comorbidities and present in rather poor health. Endovascular stent grafting provides a safe and reliable method to treat ABF.

One potential life-threatening complication is stent-graft infection; however, in our experience, no signs of infections were detected by postoperative scintigraphy with labeled leukocytes.

It is unclear why the infection rate for endovascular repair is minimal, but the stent graft remains in the center of the aneurysm sac well away from the actual fistula and source of contamination. Perhaps because there is minimal tissue trauma associated with the deployment of the stent graft, as opposed to open surgical repair, the excluded aneurysmal or pseudoaneurysmal cavity is less likely to become contaminated or infected.

Postoperative antibiotic treatment differs completely among the various authors, both with regard to the antibiotic (cephalosporin, vancomycin,