Estimation of Central Aortic Pressure Waveform by Mathematical Transformation of Radial Tonometry Pressure Data

To the Editor:

Chen et al report on the estimation of central aortic pressure waveform data using a generalized transfer function (TF). Their conclusion that “central aortic pressures can be accurately estimated from radial tonometry with the use of a generalized TF” is not supported by their data.

Intra-aortic and radial artery pressure data, collected from a cohort of 20 patients undergoing cardiac catheterization, were used to generate the TF. To use these same data to test out the TF is only appropriate for checking the internal validity of the mathematical transformations being applied. To be able to draw any useful conclusions about the overall applicability of such a generalized TF and its external validity requires further data to be prospectively collected from a separate group of patients (ie, different from those used to generate the original TF).

The application of generalized TFs using both applanation tonometric data from the radial artery and Finapres data from the digital artery suggests that when such prospective analyses are carried out, quite marked differences between estimated and measured central aortic pressures can be observed (B.T. Plunkett et al, unpublished data, 1996). Furthermore, with increasing blood pressure these differences become even more significant, with implications for the validity of such approaches in hypertensive patients.

Although Chen et al highlight the utility of this approach because “peripheral pressures can be measured noninvasively,” their noninvasively recorded peripheral pressure measurements had to be recalibrated to invasively measured data. Calibration experience with both radial tonometry and Finapres data collection suggests that these calibration errors can be substantial. Recalibration of such recordings to invasively collected data precludes application of the technique in outpatient or ward settings—the very places where most clinicians will be seeking to apply such techniques.

For these reasons, individualized TFs relying solely on noninvasive data collection (eg, simultaneous real-time carotid artery tonometry and Finapres), as some researchers have described,4 may actually permit more accurate resynthesis of central aortic pressure wave contours than generalized TFs.

There is a need for simple prospective studies to be reported from different groups of patients from those who provided data for the original creation of such generalized TFs. In this respect, it would be interesting to know how accurately the generalized TF of Chen and colleagues was able to predict central aortic pressures in the next 20 patients who were studied in their cardiac catheter laboratory. If they can calibrate these data solely using noninvasive pressure measurements, such as can be done on the ward or in the clinic, this would begin to offer useful information about the reliability of such a generalized TF. Without such prospective data and external validity checks, it is premature to make claims about “clinically acceptable accuracy.”

Eldon D. Lehmann, MB, BS, BSc
Department of Imaging, Imperial College
National Heart and Lung Institute
Royal Brompton Hospital
London, UK


Response

Dr Lehmann raises 2 concerns: (1) that broad applicability of the general transfer function (GTF) was inadequately tested because it was derived and applied to the same study group and (2) that we calibrated tonometry signals to central pressures, whereas peripheral calibration is clearly required for noninvasive implementation.

Testing the GTF in the same patient group from which it was derived did not compromise the 2 primary goals of our study: to determine if a GTF averaged from many patients performed adequately compared with individualized TFs from each patient (model robustness) and to test if a GTF derived under 1 condition (steady state) predicted data obtained under very different conditions (preload reduction) (predictive performance). Our study design did prevent predictive bias but did not eliminate interpatient variance. If differences between individual TFs (which were present and demonstrated by standard deviation about the GTF) were as critical to net TF performance as Dr Lehmann suggests, the variance of measured versus estimated pressure differences using the GTF would have been larger. In reality, they were quite small.

Furthermore, if changes in flow and mean pressure critically altered the TF, the GTF model would fail to predict responses during vena caval occlusion. We fully agree that predictive accuracy should also be tested in an independent group and have since performed such analysis (B. Fetics, BE, et al, unpublished data, 1998), applying the GTF from our prior study1 to 19 different patients. We again find close agreement between estimated and measured aortic systolic pressures (Psys): Psysmeasured = 1.02 × Psysestimated − 5.1, r = 0.995, P < 10^{-6} (SEE = 0.63 mm Hg); arterial compliance (C): Cmeasured = 1.1 × Cestimated − 0.007, r = 0.9, P < 10^{-6} (SEE = 0.053 mL/mm Hg); and good agreement between temporal waveforms (MSE = 2.6 ± 0.22 mm Hg).

There is no argument that individual patient TF differences exist, and for some estimation parameters, such as augmentation index or dicrotic notch definition, these differences likely preclude reliable use of a GTF. However, for many other useful parameters, such as systolic and pulse pressures and diastolic decay waveshape, TF differences do not appear critical to obtaining good estimates with clinically acceptable levels of accuracy. We again caution that our data are directly relevant to supine patients at rest and during preload reduction. It remains possible that greater discrepancies in the TF exist during exercise or with marked changes in systemic vascular resistance, and this will need further testing.
Regarding the second point, our goal was not to validate methods for noninvasive peripheral estimation of arterial systolic and diastolic pressures. Errors in noninvasive calibration, easily detected by mean pressure differences between cuff and central pressures, would have artificially enhanced interpatient TF variability. Our aim was to determine variability of the transform itself assuming correct calibration. Subsequent sensitivity analysis revealed only small errors in estimated systolic pressures for a ±10 mm Hg calibration error. Several methods for external pressure calibration exist and can work,2 and ongoing studies are using such methods. We too look forward to further studies of the GTF and testing of its applicability in the outpatient and ward settings, much the same as Dr Lehmann does.

David A. Kass, MD
Chen-Huan Chen, MD
Erez Nevo, MD, DSc
Barry Fetics, BE
Peter H. Pak, MD
W. Lowell Maughan, MD
Division of Cardiology
Department of Internal Medicine
Johns Hopkins University Medical Institutions
Baltimore, Md

Frank C.P. Yin, MD
Biomedical Engineering Department
Washington University in St Louis
St Louis, Mo


Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock

To the Editor:

With great interest, we have read the article of Landry and colleagues1 on the role of vasopressin deficiency in septic shock. The septic response represents a cascade of multiple physiological and metabolic changes. The complex mechanism leading to vasodilatation in septic shock is one branch of this cascade investigators are eager to elucidate. Landry et al clearly show that vasopressin plasma levels are inappropriately low in septic shock and that this deficiency contributes to the hypotension of vasodilatory septic shock. They conclude that an impaired baroreflex-mediated vasopressin secretion is the most likely explanation.

In our opinion, one other branch of the cascade should be added to the discussion. Septic shock is accompanied by activation of the hypothalamic-pituitary-adrenal axis, as demonstrated by increased serum cortisol concentrations with mean levels varying between 655 and 1665 nmol/L.2,3 This hypercortisolemia seems to be a necessary physiological response to critical illness. Cortisol augments glucose mobilization to meet energy needs, seems to be a necessary physiological response to critical illness.

Cortisol augments glucose mobilization to meet energy needs, and improves cardiac function by increasing myocardial β-adrenergic receptors. Furthermore, cortisol potentiates the vasoconstrictor actions of catecholamines and plays a vital supportive role in maintenance of the vascular tone (endothelial integrity and vascular permeability) and the distribution of total body water within the vascular component.4 The latter is an interesting phenomenon with regard to the findings of Landry et al. Boykin et al5 investigated the effect of cortisol replacement on the response of adrenalectomized dogs to water loading. They clearly demonstrated that cortisol suppresses the secretion of vasopressin and enhances free water clearance. Therefore, it might be possible that the impaired vasopressin secretion Landry et al found in the vasodilatory septic shock group is caused by hypercortisolemia.

In our opinion, it would be interesting to see whether the 2 patient populations Landry et al investigated show differences in serum cortisol concentrations.

S.E. Buijk, MD
H.A. Bruining, MD, PhD
Department of General Surgery
University Hospital Rotterdam
The Netherlands


Response

We thank Drs Buijk and Bruining for their thoughtful comments on the possible role of cortisol in determining plasma vasopressin in shock. In adrenalectomized dog, Boykin et al5 had found that glucocorticoid deficiency increased plasma vasopressin, most likely due to stimulation of baroreceptor-mediated vasopressin secretion. Thus, this study provided no answer to the question of whether excessive levels of glucocorticoids might suppress vasopressin levels. Recently, however, Papanek et al6 found a direct inhibitor effect of glucocorticoids on vasopressin secretion by the neurohypophysis. Thus, we agree with Drs Buijk and Bruining that the effect of cortisol on vasopressin levels in sepsis should be examined.

Juan A. Oliver, MD
Associate Professor of Clinical Medicine
Donald W. Landry, MD, PhD
Associate Professor of Medicine
Columbia University
College of Physicians & Surgeons
Department of Medicine
New York, NY


Heart Rate Increases in Tilt Test

To the Editor:

Mallat and colleagues have recently reported the predictive value of an early rise in heart rate during a Westminster tilt test (Circulation. 1997;96:581–584). They used a selected patient population and made an interesting observation that a rise in heart rate of >18 bpm almost invariably predicted those patients
who would subsequently have a positive test. This observation is consistent with the current theories of the mechanism of syncope.

In our center, we use the Westminster protocol for tilt testing and have reviewed the last 110 documented cases studied in our laboratory. We applied Mallat’s criteria to the 28 positive and 76 negative tests, excluding 6 patients with permanent pacemakers. This produced 16 false-negative and 19 false-positive results, which gives a sensitivity of 43% and a specificity of 39%.

We were therefore disappointed that our findings appear to contrast sharply with those reported. Clearly unlike Mallat’s study, our patients were not a selected population, but if such criteria are to be clinically useful, they need to be generally applicable. Exclusion of 40% of the population because of comorbidity significantly limits such criteria. However, using Mallat’s exclusion criteria, the sensitivity and specificity were still unacceptably low at 50% and 40%, respectively.

One does have to question the suggested clinical relevance of such an observation: is the tilt test to be abandoned after 6 minutes of tilt? Although the test is laborious, is the clinician to terminate the test early when, by Mallat’s figures, there is the potential to make a false-negative result in 1 in 8 patients? We cannot agree that it is tenable to reduce a test that lasts over an hour by 20 minutes at the expense of missing or misdiagnosing a significant number of patients.

Mallat does confine his conclusions to patients who do not go on to develop syncope and hence avoids his 1-in-8 false-negative rate. However, this has the consequence of the clinician not knowing which patients can have the tilt test curtailed until after the first 26 minutes of the test. Pragmatically, this means that increasing the number of patients in a given clinical session is not.

Finally, our data do not confirm our observations and suggest a high false-positive rate. We would be interested to hear the experience of other centers.

**Response**

We appreciate the opportunity to reply to Dr Newby and colleagues. We think that their interpretation of our results is confusing. First, they misunderstood that the main observation of our study (Circulation. 1997;96:581–584) was that “a rise in heart rate of >18 bpm almost invariably predicted . . . a positive test.” However, our observation was that a rise in heart rate (HR) of ≤18 bpm (after strict application of our inclusion criteria) during the first 6 minutes of tilt has a high predictive value for a negative tilt test. The 2 assertions are not equivalent, and definitions for false-negative and false-positive results would be different. In their interpretation, a false-positive result is a negative tilt test after a rise in HR >18 bpm. However, in our study, a false-positive result is a positive tilt test with a rise of HR of ≤18 bpm. Second, given the number of positive and negative tests and the number of false-negative and false-positive results in their retrospective study, the reported values of sensitivity or specificity are incorrect. Third, according to our criteria, false-negative results could not be missed, as we did not propose to abandon the tilt test when the increase in HR is >18 bpm.

The results of the retrospective analysis by Newby et al differ from ours. Unfortunately, several issues are not clarified. For example, we do not know from their letter whether they included patients with recurrent vasovagal syncope, whether they are confident that relatively stable continuous measurements of HR were obtained in all their patients, or whether the increase in HR (as defined in our study) was measured in a blinded manner. In addition, although they excluded patients with comorbidity, we do not know whether patients with drug use have also been excluded from their analysis. Most importantly, we do not know how many patients with positive tilt tests showed a trend for decreased HR or blood pressure during the early tilt. As mentioned in our study, such patients were excluded because of a high probability for a positive tilt. Indeed, all patients with these characteristics had positive tilt tests in our study (with a rise in HR of ≤18 bpm). The proportion of such patients may be highly variable. In the absence of more information from Newby et al, we cannot comment further on their results.

Our study was conducted in a single center and included a relatively limited number of patients. However, the results were striking and are still reproducible in our center. We are eager to know whether they are reproducible in a multicenter study including a large population of selected patients using our strict inclusion and exclusion criteria. Meanwhile, standard protocols should be the rule.

Ziad Mallat, MD
Robert Frank, MD
Centre de Rythmologie et de Stimulation Cardiaque
Hopital Jean Rostand
Ivry-sur-Seine, France

**Diagnostic Issues and Indications for Surgery in Patients With Pulmonary Artery Sling**

To the Editor:

This letter is in reference to the brief article entitled “Combined Pulmonary Artery Angiography and Tracheobronchography in Pulmonary Artery Sling,” authored by Joachim Freihorst and Thomas Paul (Circulation. 1997;96:2079). The authors reported their evaluation of a 12-month-old child with inspiratory and expiratory stridor. Barium swallow showed an anterior impression of the esophagus (consistent with a pulmonary artery sling). Two-dimensional echocardiogram could not visualize the origin of the left pulmonary artery. The authors proceeded to do combined pulmonary angiography and tracheobronchography to diagnose the pulmonary artery sling. The figure showing the combined contrast injection in the pulmonary artery and lower trachea is a nice demonstration of pulmonary artery sling, but in my experience, these are 2 unnecessary studies. In our recent experience, the diagnosis of pulmonary artery sling has been possible in all cases with a comprehensive echocardiographic analysis. We reviewed 19 cases of pulmonary artery sling operated on over a 26-year period (1970–1996). Pulmonary arteriography demonstrated the pulmonary artery sling in 7 of 10 patients (70%). This procedure has not been performed at our institution since 1991. Two-dimensional color Doppler echocardiogram using suprasternal/high-parasternal sweeps diagnosed pulmonary artery slings in 7 of 7 patients (100%). Color Doppler demonstrated the site of take-off, course, and relative size of the left pulmonary artery as it arose from the right pulmonary artery. Tracheobronchography was not performed on the patients, but rather preoperative or intraoperative bronchoscopy was performed in all cases to rule out associated complete tracheal rings, which were present in 11 (58%) of the 19 patients. We concluded that in preparation for surgery, the diagnosis of pulmonary artery sling may be confidently made from echocardiography alone. Angiography is no longer indicated to diagnose pulmonary artery sling.

In addition, according to the article, this patient has not yet had surgical intervention, but “is doing well on physical therapy and close clinical follow-up.” Our recommendation has been that all
children with respiratory symptoms and a pulmonary artery sling should have such malformations repaired at the time of diagnosis. This particular child has both inspiratory and expiratory stridor, which have been present since birth. In addition, the bronchoscopy shows severe tracheal stenosis. We have recommended operative repair in all patients through a median sternotomy approach with extracorporeal circulation and reimplantation of the left pulmonary artery anterior to the trachea. The early results of this series (12 patients) were reported in 1992. 

Our experience with pulmonary artery sling surgery now includes 22 patients. There have been no operative deaths in this series. There were 2 late deaths, both in patients with associated complete tracheal rings and complex tracheal reconstruction. The other patients have all had a complete resolution of their symptoms. My recommendation in a child with a pulmonary artery sling in all cases would be repair at the time of diagnosis.

In summary, it is my feeling that pulmonary artery angiography and tracheobronchography are rarely, if ever, indicated in patients with pulmonary artery sling. These patients should be evaluated with echocardiography and bronchoscopy. In addition, it is my strong feeling that all patients with symptoms and a pulmonary artery sling should have such malformations repaired at the time of diagnosis and should not be cared for with medical management.

Carl L. Backer, MD  
Children’s Memorial Hospital  
Chicago, Ill


Response

We appreciate the comments of Dr Backer about the feasibility of 2-dimensional echocardiography in the diagnostic workup of patients with pulmonary artery sling. We believe, however, that pulmonary angiography is still a helpful tool in establishing the correct diagnosis, since echocardiography alone may not always be 100% predictive even in experienced centers. 

Pulmonary artery sling is such a rare entity that each center should keep and follow the procedures it feels most comfortable with. In patients with pulmonary artery sling diagnosed or suspected by echocardiography, we proceed with combined angiography and tracheobronchoscopy as well as tracheobronchography. In our experience, pulmonary artery sling could be diagnosed by angiography in all 12 patients evaluated during the last 20 years. Preoperative simultaneous examination of the tracheobronchial anatomy by tracheobronchoscopy and tracheobronchography is essential for planning the optimal surgical procedure for each individual patient.

We believe that surgical treatment is not always necessary in patients with pulmonary artery sling. Indication for surgical intervention should be made on an individual basis according to the severity of symptoms and results of lung function studies. Some children with pulmonary artery sling may have normal physical capacity and development with only minor respiratory problems without surgery, as demonstrated in our patient.

Joachim Freihorst, MD  
Thomas Paul, MD  
Children’s Hospital  
Hannover Medical School  
Hannover, FR Germany

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Eldon D. Lehmann

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