Shimizu and colleagues¹ have demonstrated that both VPI and tumor size had a significant impact on survival for patients with NSCLC in univariate analysis. However, tumor size failed to be a predictor of survival in multivariate analysis, whereas VPI was still a significant predictor for all patients with NSCLC ($P < .001$) and those with stage I disease ($P = .0104$). VPI overwhelmed tumor size as a prognostic factor for NSCLC in their study. However, most studies in the literature have reported tumor size as a significant prognostic factor in NSCLC. The International Association for the Study of Lung Cancer Lung Cancer Staging Project Committee has recommended that T1 tumors be classified as T1a (≤ 2 cm) and T1b (> 2 to ≤ 3 cm) and that T2 tumors be classified as T2a (> 3 to ≤ 5 cm), T2b (> 5 to ≤ 7 cm), and T3 (> 7 cm).⁵ However, revision of non-size-based T2 descriptors has not been recommended because of the small number of patients, inconsistent clinical and pathologic results, or lack of validation.⁵ Their proposal emphasized the prognostic value of tumor size in NSCLC. Shimizu and colleagues¹ have also demonstrated that VPI was significantly associated with tumor size. We wonder how the authors dealt with the interaction of the 2 variables in multivariate analysis and interpreted the greater effect of VPI on survival in their study.

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doi:10.1016/j.jtcvs.2008.12.053

SERUM BRAIN NATRIURETIC PEPTIDE FOR PREDICTION OF SUCCESSFUL MEDICAL TREATMENT OF PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS

To the Editor:

We read with great interest the report by Tschuppert and colleagues¹ entitled "The Effect of Ductal Diameter on Surgical and Medical Closure of Patent Ductus Arteriosus in Preterm Neonates: Size Matters" and the relevant letter by Giardini and colleagues.²

Although Tschuppert and colleagues suggested that the size of a patent ductus arteriosus (PDA) can be used to predict patients in whom medical management is likely to fail to achieve hemodynamic irrelevance, Giardini and colleagues claimed that the difference in PDA diameter in patients who did and did not respond to

medical treatment was extremely low and questioned how such a small difference can be clinically significant.²

We would like to add some comment regarding factors other than PDA size to predict successful medical treatment according to our pilot study.

Recent reports suggesting that serum brain natriuretic peptide (sBNP) levels are parallel to the severity of PDA³⁻⁵ prompted us to investigate the relationship between the dose of indomethacin and the levels of sBNP or maximum diameter of PDA by ultrasound cardiography (USCG) during the first week of life. Indomethacin was repeatedly (1–4 times) administered intravenously at a single dose of 0.1 to 0.2 mg/kg until the closure of the PDA was confirmed by USCG. sBNP was measured by a commercially available kit using fluorescent immunoassay ("Shiono-Spot," Shionogi Pharmaceutical Co, Osaka, Japan). The required blood volume is only 70 μ L, and a result can be obtained within 15 minutes with this kit.

There was a significant relationship between the peak levels of sBNP within 5 days of life and the total dose of indomethacin ($n = 8$, $r = 0.78$, $P < .05$, Table). Notably, the required total dose of indomethacin to close a symptomatic PDA was 0.1 to 0.2 mg/kg in the infants with sBNP levels less than 1000 pg/mL, whereas the required dose was 0.3 mg/kg or more in those with higher sBNP levels (> 2000 pg/mL), as shown in Table 1.

TABLE 1. Relationship among serum levels of brain natriuretic peptide, size of patent ductus arteriosus, and total dose of indomethacin

Case no.	Gestational age (wk)	Total dose of indomethacin (mg/kg)	Age at PDA closure* (d)	Peak levels† of sBNP (pg/mL)	Maximum diameter of PDA (mm)
1	27.7	0.1	5	640.4	1.5
2	27.7	0.2	8	40.9	1.2
3	31.4	0.2	3	83.2	1.4
4	28.0	0.2	3	796.5	1.5
5	28.7	0.2	3	152.3	2.1
6	28.7	0.3	16	> 2000	2.1
7	29.9	0.6	5	> 2000	3.9
8‡	29.9	0.7	14	> 2000	3.3

PDA, Patent ductus arteriosus; sBNP, serum brain natriuretic peptide. *Confirmed by ultrasound echocardiography.

†Measured within 5 days of life. ‡PDA reopened at the age of 16 days and received surgical ligation.

Furthermore, closure of the PDA occurred within 10 days in all of 5 infants demonstrating lower levels of sBNP (<1000 pg/mL), whereas closure occurred in only 1 of 3 infants with higher levels (>2000 pg/mL): One infant who required the largest dose of indomethacin finally required operative ligation for the PDA because it reopened (case number 8 in Table 1).

From these findings, we suggest that the hemodynamic severity of the PDA in addition to the size of the PDA should be taken into consideration to predict the possibility of successful medical treatment and to seek the timing of surgical intervention because no single parameter can be a complete index. The measurement of sBNP in the early postnatal days can be adjunctive and useful for these purposes because it is rather objective than the measurement of PDA diameter by USCG and requires only a small blood sample.

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MECHANISM OF MYOCARDIAL PROTECTION BY PRESSURE-VOLUME UNLOADING INVOLVES STRETCH-INDUCED PATHOPHYSIOLOGY

To the Editor:

I read with interest the recent report by Tamareille and colleagues,¹ who demonstrate in a porcine model of myocardial infarction that left ventricular (LV) unloading with a left ventricular assist device (LVAD) during early reperfusion is associated with both reduced endothelin-1 release by the myocardium and reduced infarct size. They demonstrate a positive correlation between early post-ischemia endothelin release and infarct size but admit that a cause-effect relationship was not established by this study. They found no effect of LV unloading on regional myocardial blood flow. Our laboratory previously demonstrated that LV unloading during early reperfusion ameliorates myocardial stunning in a canine model of regional ischemia-reperfusion.² As did Tamareille and colleagues, we found no differences in regional myocardial blood flow between LVAD-treated and untreated animals. By using ultrasonic dimension crystals, however, we observed marked ischemia-induced segmental stretch during both systole (paradoxical bulging) and diastole (creep), phenomena that were completely eliminated by LV pressure-volume unloading. We hypothesized that LVAD-

mediated alleviation of abnormal stretch was responsible for improved contractile function. We later tested this hypothesis in an isolated guinea pig papillary muscle model,³ in which we demonstrated that abnormal stretch caused contractile dysfunction similar to stunning. This dysfunction was abolished by gadolinium, a lanthanide cation that blocks a variety of stretch-induced perturbations in cardiac function through mechanisms that may involve specific stretch-activated ion channels. We then returned to the canine model and demonstrated that gadolinium attenuates regional stunning to the extent of mechanical LV unloading.⁴ I would therefore suggest to the authors that the mechanism of infarct reduction with LV unloading observed in their study was not reduced endothelin release, but the elimination of abnormal stretch, which also happened to reduce endothelin release.

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