SERIAL IMPEDANCE PLETHYSMOGRAPHY FOR DIAGNOSIS OF SYMPTOMATIC VENOUS THROMBOSIS

To the Editor: The recent prospective studies by Huisman et al. (March 27 issue)[1] and Hull et al.[2] suggest that in both hospital and community settings, serial impedance plethysmography can effectively substitute for contrast venography in the evaluation of patients with clinically suspected deep-vein thrombosis. Previous investigations have demonstrated impedance plethysmography to have a sensitivity of 95 percent and a specificity of 96 percent in the diagnosis of proximal-vein thrombosis.[3] Such studies have generally been performed in academic centers having extensive experience with impedance plethysmography. Although impedance plethysmography is more objective and less operator-dependent than other noninvasive diagnostic techniques for proximal-vein thrombosis, its accurate application still requires careful attention to detail.[3] Before using it as the sole diagnostic test in patients with suspected deep-vein thrombosis, medical centers should first document adequate sensitivity and specificity (i.e., above 90 percent for each measure) of impedance plethysmography for proximal-vein thrombosis in their institution by performing contrast venography along with the impedance studies. The necessity of this approach is emphasized by two recent studies demonstrating sensitivities of only 63 percent[4] and 86 percent[5] and specificities of 83 percent[4] and 76 percent[5] of impedance plethysmography in the diagnosis of proximal-vein thrombosis. Anecdotal experience from our own institution supports the need to document the accuracy of impedance plethysmography.

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To the Editor: I was disappointed with the report of Huisman et al. for two reasons. First, they showed a decreasing frequency of positive plethysmograms over time, with only 2 percent of the total cases of thrombosis detected on day 10. Given the low yield, was it necessary to follow the patients for the full 10 days, or would 5 days (or even 2) have sufficed? Second, as a matter of interest, where were the venographically demonstrated thrombi located? Were all the noninvasively detected clots proximal to the popliteal fossa or were some (and what percentage) located more distally?

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The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: The accuracy of impedance plethysmography depends critically on obtaining maximal venous filling during the temporary occlusion of venous outflow. Hull et al. have optimized the reliability of impedance plethysmography by increasing the cuff-occlusion time and sequential testing.[1] In their study, it was noted that as venous filling increased, there was a corresponding increase in both the sensitivity and the specificity of the test. Dr. Stults and colleagues report on low sensitivities (63 and 86 percent) and specificities (83 and 76 percent) in two studies that compound impedance plethysmography with contrast venography.

In the study by Satiani et al.,[2] it is unclear whether the authors used the sequential testing described by Hull and colleagues. This might have greatly influenced the reported sensitivity and specificity, because all the patients with false negative impedance plethysmography results in their study were shown to have nonocclusive proximal venous thrombosis in the femoropopliteal area. As reported by Hull et al.,[1] most of these nonocclusive proximal venous thrombi are diagnosed by obtaining optimal venous filling. It is also unclear whether the patients with false negative results were symptomatic or asymptomatic.

It is acknowledged that impedance plethysmography is most sensitive in detecting symptomatic, totally occlusive proximal-vein thrombi. The sensitivity for asymptomatic proximal-vein thrombi is reported to be 83 percent.[3]

In the investigation by Ramchandani et al.,[4] a heterogeneous group of inpatients (65 percent) and outpatients (35 percent) was studied; some of the patients were not symptomatic but were screened because they were at risk of deep-vein thrombosis. Of nine patients with serious thrombosis after hip surgery, all were asymptomatic and seven had false negative impedance plethysmography studies. Seven of the 15 patients with proximal deep-vein thrombosis and false negative impedance plethysmography tests had nonoccluding clots. It remains unclear whether these patients were symptomatic or asymptomatic.

We agree with Stults and Dere that accurate impedance plethysmography requires continued careful attention and thorough training of technicians. The sensitivity and the specificity of the procedure must be evaluated separately for confirming the diagnosis in symptomatic patients and for screening in patients with a high risk of deep-vein thrombosis.

In reply to Dr. Saglio, we refer to the Discussion section of our article, where we state that the yield of positive plethysmograms was progressively smaller during the subsequent tests, and since only 2 percent of the abnormal plethysmograms were obtained on day 10, the need for repeated testing until that time could be debated and is currently under investigation in our hospital. The thrombi demonstrated by venography were, as stated in the Results section, located both proximally and distally in 89 percent of the patients and distally only in 11 percent of the patients.

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CORRELATION OF LEFT VENTRICULAR EJECTION FRACTION AND PLASMA ATRIAL NATRIURETIC PEPTIDE IN CONGESTIVE HEART FAILURE

To the Editor: It has recently been demonstrated that the plasma concentration of atrial natriuretic peptide (ANP) is increased in congestive heart failure.[1-5] We have compared the plasma concentration of ANP with the ejection fraction measured by radionuclide ventriculography in a group of patients with a clinical diagnosis of congestive heart failure.

Fifteen patients admitted because of congestive heart failure consented to measurement of plasma ANP, and 10 underwent radionu-

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clide ventriculography within 48 hours of the sampling for ANP. Four of the 10 were in the New York Heart Association functional class I or II, and 6 in class III or IV. Radionuclide ventriculography was performed with equilibrium multiple-gated acquisition blood-pool analysis to determine the left ventricular ejection fraction.[6] Plasma ANP was measured by radioimmunoassay of plasma acidified to pH 4 with 4 percent acetic acid, extracted by passage through Sep-Pak C-18 cartridges (recovery, 78 percent), eluted with ethanol acidified to pH 4 with 4 percent acetic acid, evaporated in a Speed-Vac, and resuspended in 0.5 ml of 0.1 M sodium phosphate buffer (pH 7.4) containing 0.05 M sodium chloride, 0.1 percent bovine serum albumin, 0.1 percent Triton X-100, and 0.01 percent sodium azide. A nonequilibrium radioimmunoassay was performed with a second antibody, and polyethylene glycol was used for separation of bound and free tracer. The tracer was ^{125}I-labeled human ANP prepared by the lactoperoxidase method. The antibody was from Peninsula (Belmont, Calif.), with 100 percent cross-reactivity with human α-ANP, rat ANP, and atriopeptin III, 27 percent with atriopeptin II, and 3 percent with atriopeptin I. The lowest detectable concentration of ANP was 3 pg per tube; the IC_{50} of the standard curve was 32 pg per tube. The intraassay variation was 12.7 percent, and the interassay variation was 6.7 percent. The plasma concentration of ANP in eight control patients (six men and two women 62±3 years old [range, 54 to 75]) was 14±3 fmol per milliliter (range, 4 to 30). In the 15 patients with congestive heart failure (8 men and 7 women in functional classes I through IV, 64±2 years old [range, 54 to 76]) plasma ANP was 95±21 fmol per milliliter (range, 23 to 330) — significantly higher than in controls ($P < 0.005$), in agreement with previous data.[1-5] In the 10 patients with heart failure, the left ventricular ejection fraction was inversely correlated ($r = 0.93$, $P < 0.005$) with the plasma ANP concentration (Fig. 1).

The left ventricular ejection fraction has been shown to have an excellent correlation with invasively determined indexes of left ventricular function.[7,8] Plasma ANP is also increased after sodium loading,[2,9] during atrial tachyarrhythmias,[10,11] in chronic renal failure,[12] and in primary hyperaldosteronism and Bartter's syndrome.[13] If these conditions are excluded, measurement of plasma ANP may become a useful tool in the follow-up of patients with congestive heart failure.

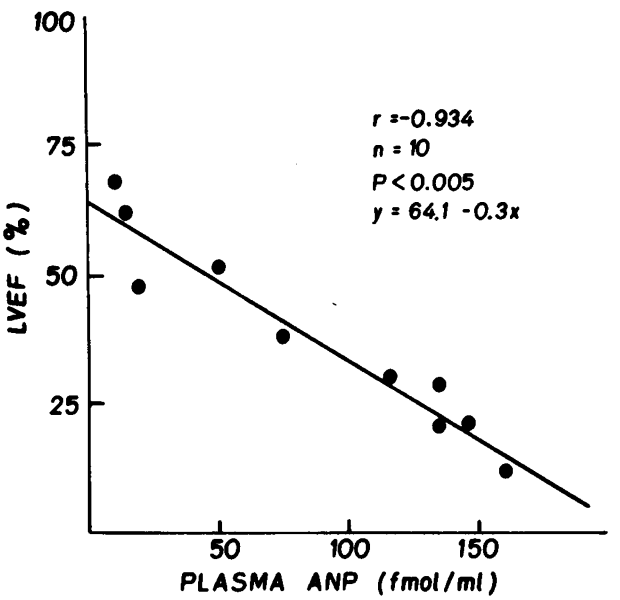

Figure 1. Correlation of Left Ventricular Ejection Fraction (LVEF, Measured by Gated Blood-Pool Analysis of Radionuclide Ventriculogram) and Plasma Concentration of Atrial Natriuretic Peptide (ANP) in 10 Patients with Congestive Heart Failure.

To convert ANP values to picograms per milliliter, multiply by 3.

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MORE ON ZELLWEGER'S SYNDROME, INFANTILE REFSUM'S DISEASE, AND RHIZOMELIC CHONDRODYSPLASIA PUNCTATA

To the Editor: Wanders et al.[1] report in the March 20 issue that somatic-cell fusion between fibroblasts from patients with Zellweger's cerebrohepatorenal syndrome and fibroblasts from patients with infantile Refsum's disease fails to correct the dihydroxyacetonephosphate–acyltransferase deficiency that these cell lines manifest. Fusion between either of these cell lines and fibroblasts from patients with rhizomelic chondrodysplasia punctata corrects the deficiency. Dihydroxyacetonephosphate–acyltransferase activity is severely diminished in rhizomelic chondrodysplasia punctata, but intact peroxisomes are present in fibroblasts.[2] Although the possibility was considered that complementation could not occur in Zellweger's syndrome and Refsum's disease because of the absence (or paucity) of preexisting peroxisomes, the results of these fascinating experiments were interpreted to indicate that these disorders are caused by allelic mutations or are phenotypic variants of the same mutation.[1]

In the absence of a cellular mechanism for de novo membrane synthesis, it does not appear to be possible to interpret the genetic implications of these fusion experiments. New membrane formation is accomplished by the insertion of proteins and lipids into preexisting membrane. This may occur by the incorporation of newly formed macromolecules synthesized by cytoplasmic polysomes, as occurs in peroxisomes,[3] or the fusion of segments of membrane from one organelle with other such secretory vesicles and plasma mem-

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