chest tube was inserted. Chest drainage continued for several days, with excessive serous fluid losses and decreased plasma protein (4.4 g/dL) and fibrinogen (71.3 mg/dL) levels. Fibrinogen (200 mg/kg per day for 2 days) was administered again, and the fluid leakage stopped completely within 2 days. On the basis of a high D-dimer level (736 ng/mL) detected after the second fibrinogen administration, we speculated that the fibrinolytic system had been greatly amplified in this cyanotic patient. Therefore, we started an oral medication of tranexamic acid (Transamin-G; Dai-Ichi, Inc, Tokyo, Japan) 30 mg/kg daily as an antifibrinolytic therapy. Additional prophylactic fibrinogen infusion was achieved twice at 2-week intervals. Since then, the plasma fibrinogen level has been within normal range (no less than 170 mg/dL), and the plasma D-dimer level has been maintained at a relatively lower level (200 to 600 ng/mL), leaving the patient in stable condition without any fluid leakage. Neither thrombocytopenia nor bleeding tendency was observed. No thrombotic events occurred. A bidirectional Glenn shunt was successfully done 6 months after the B-T shunt.

LeBlanc and associates² first described excessive fluid leakage after a modified B-T shunt. Bolton and Cannon³ suggested that rapid wetting of the graft with organic solvents or a high blood flow with faulty formation of fibrin may be responsible for the leakage. However, the mechanism still remains unclear. In most of the cases previously described, conservative management failed and surgical interventions were required. Maitland and coworkers⁴ reported 2 cases in which leakage was controlled with intraluminal fibrin glue. Noyez and Daenen¹ reported the case of a patient treated with fibrin glue and collagen fleece wrapping. Intravenous fibrinogen administration was first described by Suzuki and associates⁵ as an effective conservative management of the leakage. Human fibrinogen products were originally developed for congenital fibrinogenopenia and are commercially available in Germany and Japan. According to their report, 7 patients were successfully treated with fibrinogen administration (150-200 mg/kg per day for 3 or 4 days), and in 2 of those cases the plasma fibrinogen level was much lower than the normal range at the beginning of the leakage. As we described, the fact that plasma fibrinogen level decreased and plasma D-dimer level increased at the beginning of the fluid losses may be an important clue to the mechanism of leakage. We speculate that the fibrinolytic system could be greatly amplified in some cyanotic patients with polycythemia against great thrombotic tendency owing to high blood viscosity. A probable explanation is that the fibrin cross-linking step and newly formed fibrin clots in a PTFE graft wall could be easily impaired and degraded when this overwhelming fibrinolytic regulation occurs. Once the strong fibrinolysis begins, a large amount of fibrinogen may need to be supplied until newly formed cross-linked fibrin is tightened and subsequent clot formation is completed. Platelet function of patients with polycythemia may play another important role in this problem. In our preliminary data of the patients, very weak aggregation and poor α -granule release response have

been observed. We hypothesize that both strong fibrinolytic response and weakened platelet function could be the physiologic adaptation phenomenon against the great thrombotic risk. Intravenous fibrinogen administration is effective and the combination of fibrinogen and antifibrinolytic therapy may be the best conservative management available for serous leakage through PTFE so far. Further investigations are needed to prove our hypothesis.

Yuji Hiramatsu, MD
Naotaka Atsumi, MD
Akinobu Sasaki, MD
Toshio Mitsui, MD
Department of Surgery
Institute of Clinical Medicine
University of Tsukuba
1-1-1 Tennoh-dai
305-8575 Tsukuba-city, Japan

REFERENCES

1. Noyez L, Daenen W. The modified polytetrafluoroethylene Blalock-Taussig shunt: case report of an unusual complication. *J Thorac Cardiovasc Surg* 1987;94:634-5.
2. LeBlanc J, Albus R, Williams WG, Moes CA, Wilson G, Freedom RM, et al. Serous fluid leakage: a complication following the modified Blalock-Taussig shunt. *J Thorac Cardiovasc Surg* 1984;88:259-62.
3. Bolton W, Cannon JA. Seroma formation associated with PTFE vascular grafts used as arteriovenous fistulae. *Dialysis Transplant* 1981;10:60-6.
4. Maitland A, Williams WG, Coles JG, Freedom RM, Trusler GA. A method of treating serous fluid leak from a polytetrafluoroethylene Blalock-Taussig shunt. *J Thorac Cardiovasc Surg* 1985;90: 791-3.
5. Suzuki T, Fukuda T, Katohgi T, Oda Y. Effectiveness of fibrinogen to avoid serous fluid leakage through polytetrafluoroethylene (PTFE) tubular graft. *J Jpn Assoc Thorac Surg* 1990;38:596-600.

12/8/97767

Aortic function in patients during intra-aortic balloon pumping determined by the pressure-diameter relation

To the Editor:

Stefanadis and associates¹ provide an important analysis of aortic function in patients during intra-aortic balloon pumping, which aids in the understanding of the improved circulatory function that results from its use. However, two points need further clarification.

First, in Fig 4 they state that the fourth derivative of the aortic pressure and diameter was used to estimate (1) minimum aortic pressure and diameter and (2) the point of inflection of the aortic pressure and diameter, thus allowing calculation of the pressure augmentation index. The fourth derivative has been previously described as the optimum way of deriving these points.²

The use of the fourth derivative is against the basic principles of calculus, in which the first derivative is used to evaluate minima and maxima, with the second derivative used to distinguish between these and points of inflexion, negative at

Fig 1. Typical blood pressure tracing from a patient's aorta, and the first four derivatives (see text for explanation).

Fig 2. The effect of systemic vascular resistance on the augmented pressure produced by an intra-aortic balloon pump.

maxima, positive at minima, and zero at points of inflexion.³ The third and fourth derivatives have no use with regard to the aforementioned points. To prove this, we digitized the aortic blood pressure of a patient every 10 ms; the first four derivatives are shown in Fig 1. The first derivative crosses zero three times, indicating the maxima and two minima of the blood pressure trace. The second derivative is positive at the first and third zero point of the first derivative, indicating a minima, and is negative at the second zero point (it should be noted that the sign of the second derivative determines the maxima/minima status, and not the actual value). In addition, the second derivative is zero during the upstroke of the pres-

sure tracing, indicating that the point of inflexion occurs at this point.

Second, no measurements of systemic vascular resistance/impedance (SVR/SVI) were made, and yet the SVR and SVI have a major effect on the pressure tracing that is obtained, thus influencing the augmentation index measured. Fig 2 demonstrates the influence of SVR as measured by a thermodilution catheter (Swan-Ganz; Baxter Healthcare Corp, Edwards Div, Santa Ana, Calif) on the augment pressure generated by an intra-aortic balloon pump in 11 patients after cardiac surgery. It could be argued that the pressure augmentation index measured on the balloon pump augmentation pulse would be more accurate than on the heart ejection pulse part of the blood pressure tracing, but this remains to be validated.

Michael Poullis, MD
Department of Cardiothoracic Surgery
Hammersmith Hospital
Du Cane Rd
East Acton
National Heart and Lung Institute
Imperial College of Science
London W12 0NN, United Kingdom

REFERENCES

1. Stefanadis C, Dernellis J, Tsiamis E, Stratos C, Kallikazaros I, Toutouzas P. Aortic function in patients during intra-aortic bal-

loon pumping determined by the pressure-diameter relation. *J Thorac Cardiovasc Surg* 1998;116:1052-9.

2. Kelly R, Hayward C, Avolio A, et al. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 1989;80:1652-9.
3. Lamb H. Applications of the derived function. In: *Infinitesimal calculus*. Cambridge University Press; 1944. p. 95-125.

12/8/97769

Reply to the Editor:

Regarding the letter to the Editor referring to our article, "Aortic Function in Patients During Intra-aortic Balloon Pumping Determined by the Pressure-Diameter Relation," we would like to state the following.

First, wave reflections are evaluated by measuring augmentation index, defined as the ratio: (pressure from inflection point to late systolic peak)/(pulse pressure).¹ Beginning of pressure wave upstroke, inflection point, and late systolic peak are defined by using the fourth derivative of pressure. When plotted against derivative, the timing of inflection point is indicated by a local minimum in the first derivative. To simplify the detection of this point, higher order derivatives are used to identify the zero-crossing point equivalent to the local minimum of the first derivative. The first zero crossing of the fourth derivative (in a direction from above to below the zero line) corresponded to the beginning of the pressure wave upstroke. The second zero crossing in the same direction corresponded to the inflection point.¹ Scatter in each primary pressure derivative is smoothed by applying moving average curve (Microsoft Excel 97 for Windows; Microsoft Corporation, Redmond, Wash). This resulted in phase shifts, which depend on the interval of the moving average. Phase shifts of all derivatives are adjusted accordingly.

Second, pressure augmentation index measured on the heart ejection part of the blood pressure tracing is the only way to appreciate, in a comparative manner, the changes of the reflected waves both at baseline and during intra-aortic balloon pumping.²

Christodoulos Stefanadis, MD
Department of Cardiology
Hippokraton Hospital
9 Tepeleniou Str
Paleo Psychico
Athens 15452, Greece

REFERENCES

1. Stefanadis C, Dernellis J, Vavuranakis M, Tsiamis E, Vlachopoulos C, Toutouzas K, et al. Effect of ventricular pacing-induced tachycardia on aortic mechanics in man. *Cardiovasc Res* 1998;39:506-14.
2. Stefanadis C, Dernellis J, Tsiamis E, Stratos C, Kallikazaros I, Toutouzas P. Aortic function in patients during intra-aortic balloon pumping determined by the pressure-diameter relation. *J Thorac Cardiovasc Surg* 1998;116:1052-9.

12/8/97768

Myocardial pseudovascular tubes are present in the delayed rejection of pig-to-baboon orthotopic cardiac xenografts

To the Editor:

In the article by Xu and associates¹ dealing with the rejection of pig-to-baboon orthotopic cardiac xenografts, the authors describe microvascular thromboses in a heart that has survived 19 days after transplantation (see their Fig 4). The individual thromboses are surrounded by damaged cardiomyocytes manifesting a more or less shrunken nucleus located in the midst of a large myocytolytic vacuole or rarefied myofibrils.

Having been intrigued by the curious shapes, high number, and large diameters of the alleged microthromboses, I have found that they often contain parts of cardiomyocytes in their lumina. Using Cartesian coordinates and centimeters as units for their exact localization in Fig 4, the microthrombosis-like structures containing cardiomyocyte nuclei are located at the following points: x = 0.6, y = 4.1; x = 1.7, y = 1.8; x = 2.5, y = 2.5; x = 6.9, y = 5.6; x = 7.3, y = 3.3. The structures containing myocytolytic vacuoles with or without nuclear remains are located at these points: x = 2.4, y = 2.3; x = 3.8, y = 0.3; x = 5.8, y = 0.3; x = 6, y = 2.9; x = 6.8, y = 5.3; x = 7.5, y = 3; x = 7.8, y = 2.6. Finally, the large thrombus-like structure containing rarefied myofibrils is present at x = 7.7, y = 3.8. Consequently, the alleged microthromboses are not vascular structures but "myocardial pseudovascular tubes"² formed by individual hyalinized cardiomyocytes or their bundles.

Hyalinized cardiomyocytes may undergo apoptotic disintegration into "eosinophilic droplets" similar to red cells,^{3,4} creating an impression of interstitial hemorrhage. In Fig 4,¹ such a process is present in the form of a hook delineated by the points x = 3.5, y = 0; x = 3, y = 6; x = 7.5, y = 6.9. Note the presence of several "naked" cardiomyocyte nuclei close to the point x = 6.5, y = 6.7. Free cardiomyocyte nuclei were described in Syrian hamster cardiomyopathy⁵ and in the delayed rejection of heart xenografts.⁴ Apparently, the apoptotic disintegration of cytoplasm may precede that of the nucleus.⁶

The purpose of this letter is not to deny the presence of genuine microthromboses, which were well documented by electron microscopy in the hyperacute and delayed rejections of cardiac xenografts and allografts,⁷ but to increase the awareness of myocardial pseudovascular tubes in the same situations.

Jiri T. Beranek, MD
4101 S Wappel Dr
Columbia, MO 65203

REFERENCES

1. Xu H, Gundry SR, Hancock WW, Matsumiya G, Zuppan CW, Morimoto T, et al. Prolonged discordant xenograft survival and delayed xenograft rejection in a pig-to-baboon orthotopic cardiac xenograft model. *J Thorac Cardiovasc Surg* 1998;115:1342-9.
2. Beranek JT. Are all bizarre intramyocardial artery-like structures in human cardiac allografts really coronary vessels? *Histopathology* 1997;30:197-8.
3. Beranek JT. Apoptosis is the main mechanism of cardiomyocyte