Cardiol Young 1994; 4: 228-231

ISSN 1047-9511

Editorial

Elucidation of digital clubbing may help in understanding the pathogenesis of pulmonary hypertension associated with congenital heart defects

Manuel Martínez-Lavín

STUDY OF CYANOTIC CONGENITAL HEART DISEASES HAS now yielded data that may explain the cause of digital clubbing.[1-3] This new information may also be pertinent to the pathogenesis of the type of pulmonary hypertension which complicates congenital heart defects. Thus it has been established that a high proportion of patients with non-cyanotic congenital heart defects and left-to-right shunts develop pulmonary hypertension, eventually reversing the shunt with subsequent development of cyanosis and digital clubbing.[4] The mechanisms leading to the induction of hypertension are not fully understood. The classic histologic observations by Heath and Edwards[5] showed progressive structural changes of pulmonary microvasculature. These begin as medial hypertrophy and intimal hyperplasia, are followed by occlusion, and progress to fibrinoid necrosis.

More recent investigations have demonstrated that activation of pulmonary endothelial cells is a prominent feature of the syndrome. Rabinovitch et al[6] demonstrated electron microscopic evidence of alteration of these cells, suggesting heightened metabolic function. This impression has been strengthened by subsequent studies from the same group that focussed on the abnormal biology of von Willebrand factor.

Von Willebrand factor is a multimeric glycoprotein synthesized by platelets and endothelial cells. It plays a crucial role in adhesion of platelets to the subendothelium. Its multimers of high molecular weight adhere to platelets. High shear rates promote its action. Raised circulating levels usually reflect activation of platelets and/or endothelial cells.[7,8] Rabinovitch et al[9] reported that, in pulmonary hypertension, endothelial cells produced increased amounts of von Willebrand factor and increased circulating levels of this substance. Multimeric analysis of the circulating glycoprotein showed absence of its high molecular weight forms.[9] Similar structural abnormalities were described by Gill et al.[10] Interestingly, the latter investigators found that those patients who had undergone complete surgical correction of left-to-right shunts had normalization of the multimers, demonstrating that the structural abnormalities were acquired and reversible.

Accepted for publication 23 September 1993

Relationship to pulmonary hypertension

To test the direct effect of hypertension, Rabinovitch and her colleagues utilized pulmonary endothelial cell cultures in a pressure dome pulsated at 100/60 mm Hg at 60 times per minute. They failed to identify the production of a growth factor from the stressed cells, suggesting that high pressure alone was not sufficient to activate them.[4] Current knowledge therefore indicates that activation of endothelial cells is a prominent, but incomplete feature of pulmonary hypertension, suggesting that release of proteases and growth factors from the activated cells could play a role in the structural damage of the pulmonary microvasculature.

Relationship to digital clubbing

Recent evidence generated at our institute has suggested that localized activation of platelets and/or endothelial cells at distal parts of the systemic circulation with the ensuing release of fibroblast growth factors could be the key feature in the development of clubbing.[1-3] We have performed these studies in patients with cyanotic congenital heart diseases. This pathology is the best model with which to study the digital deformity, since practically all these children have lifelong presence of clubbing,[11] while more than a third develop the more generalized disorder of hypertrophic osteoarthropathy.[12]

No other internal illness is so highly associated with the acropachy. A particularly interesting model for the

study of clubbing is the cases with patency of the arterial duct with reversal of the original left-to-right shunt. In such instances, clubbing (and sometimes periostosis) become evident only in the cyanotic limbs that receive "unfiltered" blood. This information suggests that bypass of the lungs is the key feature in the development of clubbing.[13] The lack of demonstration of inflammatory and autoimmune phenomena by conventional serology, in addition to the excessive deposition of collagen evident in histologic studies, led to a proposal[13] that a fibroblast growth factor could be at the epicenter of the syndrome. This growth factor would normally be present in the central venous circulation and removed in the lungs. Among the growth factors, one derived from platelets was chosen on the basis of a mathematical model proposing that, in normal circumstances, large platelets are fragmented in the highly dichotomized pulmonary circulation. It was suggested that, in cases with right-to-left shunts, large thrombocytes that escaped pulmonary fragmentation would enter the systemic circulation and reach its most distal sites on axial streams, being trapped there and releasing growth factors and thus inducing clubbing.[14]

Our studies of patients with cyanotic heart defects are consistent with these explanations. These patients are frequently thrombocytopenic. In addition, they have a bizarre population of platelets characterized by the presence of macrothrombocytes with aberrant distribution curves for volume. These features demonstrate a heterogeneous population, and concur with the mathematical theory of fragmentation of platelets in the lungs.[1] Furthermore, it has been demonstrated that these cyanotic patients, and also patients with primary hypertrophic osteoarthropathy, have raised circulating levels of the antigen of von Willebrand factor.[3] As already discussed, this abnormality suggests activation of platelets and endothelial cells.

Resultant hypothesis

By joining these two avenues of investigation, a different hypothetical model for the pathogenesis of pulmonary hypertension can be suggested, with platelets taking the leading role. Patency of the arterial duct is used as prototype. In this congenital malformation, the left-to-right shunt provokes increased pulmonary flow and, thus, abnormal shear rates between fragmenting platelets and pulmonary microvasculature. In this way, the adhesive properties of von Willebrand factor are promoted. The high molecular weight fragment of the factor are adsorbed to the platelets, leaving an abnormal molecule in the circulation. If correct, this can explain the described structural abnormalities of von Willebrand factor.[9,10] As a result of this interaction, platelets and

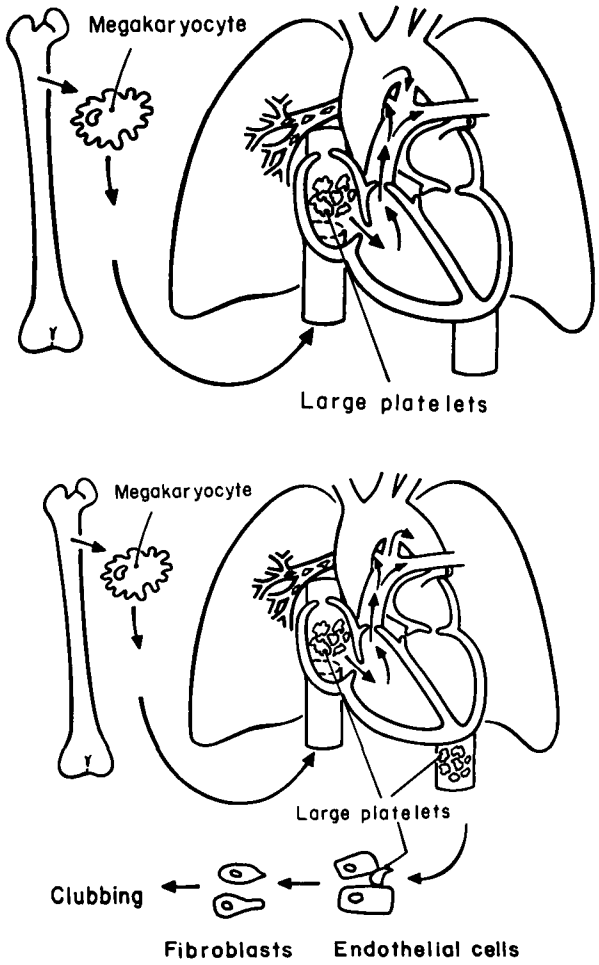

Figure. *In the hypothesis proposed for the pathogenesis of pulmonary hypertension and digital clubbing, the patent arterial duct is used as a model. Large platelets are normally fragmented in the pulmonary circulation. The shunt through the duct induces increased pulmonary flow and abnormal shear rates between thrombocytes and endothelial cells enhancing the adhesive properties of von Willebrand factor. Vascular hypertrophy takes place (Upper). If the process persists unchecked, pulmonary hypertension ensues and the flow is reversed through the duct. At this juncture, large thrombocytes are able to bypass the lung, reaching only the lower parts of the systemic circulation. They impact at its most distal sites, activate endothelial cells and induce a localized form of clubbing (Lower).*

endothelial cells are activated with the release of proteases and growth factors. These then induce structural changes in the pulmonary microvasculature (Figure). If the congenital malformation is not corrected, hypertension develops and obstruction of the lumens eventually reverses the flow through the duct. At this juncture, large platelets are able to bypass the lungs and gain direct access to the systemic circulation. Since the duct joins the aortic arch distal to the left subclavian artery, the

https://doi.org/10.1017/S1047951100011094 Published online by Cambridge University Press

platelets would reach only the lower extremities, impacting preferentially at most distal sites and there activating endothelial cells, promoting the release of their growth factors and thus inducing the localized form of clubbing typical of the patent arterial duct (Figure).

One recent report has produced evidence to support this hypothesis, Chirstman et al[15] found that patients with pulmonary hypertension had increased urinary excretion of platelet catabolites suggesting hyperactivity of these blood elements.[15]

I recognize, nonetheless, that my proposed hypothesis contains several conceptual gaps that need to be filled with solid scientific experimentation.

Instituto Nacional de Cardiología "Ignacio Chávez"
Juan Badiano 1, Tlalpan
14080 México D.F., México

References

1. Vázquez-Abad D, Martínez-Lavín M. Macrothrombocytes in the peripheral circulation of patients with cardiogenic hypertrophic osteoarthropathy. Clin Exp Rheumatol 1991; 9: 59-62.
2. Martínez-Lavín M, Piñeda C. Digital clubbing. Lancet 1990; II: 1444. [Letter]
3. Matucci-Cerinic M, Martínez-Lavín M, Rojo F, Fonseca C, Kahaleh B. von Willebrand factor in hypertrophic osteoarthropathy. J Rheumatol 1992; 19: 765-767.
4. Rabinovitch M. Pulmonary hypertension. In: Moss E (ed). Heart Disease in Children and Adolescents. Williams and Wilkins, Baltimore, 1989, pp 856-886.
5. Heath D, Edwards E. The pathology of hypertensive vascular disease. Circulation 1958: 18, 533-547.
6. Rabinovitch M, Bothwell T, Hayakawa B, Williams W, Trusler G, Rowe R, Olley P. Pulmonary endothelial abnormalities in patients with congenital heart defects and pulmonary hypertension. Lab Inv 1986; 55: 632-653.
7. Sixma J, de Groot P. von Willebrand factor and the blood vessel wall. Mayo Clin Proc 1991; 66: 628-633.
8. Meyer D, Pietu G, Fressinaud E, Girma J. von Willebrand factor; structure and function. Mayo Clin Proc 1991; 66: 516-523.
9. Rabinovitch M, Andrew M, Thom H, Truler G, Williams W, Rowe R, Olley P. Abnormal endothelial factor VIII associated with pulmonary hypertension and congenital heart defects. Circulation 1987; 76: 1043-1052.
10. Gill J, Wilson A, Endress-Brooks J, Montgomery R. Loss of largest von Willebrand factor multimers from plasma of patients with congenital heart defects. Blood 1986; 67: 758-761.
11. Vázquez-Abad D, Martínez-Lavín M. Digital clubbing; a numerical assessment of the deformity. J Rheumatol 1989; 16: 518-520.
12. Martínez-Lavín M, Bobadilla M, Casanova J M, Attié F, Martínez M. Hypertrophic osteoarthropathy in cyanotic congenital heart diseases; its prevalence and relationship with bypass of the lung. Arthritis Rheum 1982; 28: 461-475.
13. Martínez-Lavín M. Digital clubbing and hypertrophic osteoarthropathy; a unifying hypothesis. J Rheumatol 1987 14: 6-8.
14. Dickinson CJ, Martin JF. Megakaryocytes and platelet clumps as the cause of finger clubbing. Lancet 1987; II: 1434-1435.
15. Chirstman B, McPherson C, Newman J, King G, Bernard G, Groves B, Loyd J. An imbalance between the excretion of thromboxane and protacyclin metabolites in pulmonary hypertension. N Engl J Med 1992; 327: 70-75.