Clin. Lab. Haem.
2002, **24**, 161–164

The lungs and platelet production

G. ALIBERTI*, M. PROIETTA*, I. PULIGNANO*, L. TRITAPEPE†, C. DI GIOVANNI †, A. SCHIAPPOLI*, G. VERCILLO*

**Dipartimento di Scienze Cliniche, †Istituto di Chirurgia del Cuore e dei Grossi Vasi, Università 'La Sapienza', Rome, Italy*

Summary Several studies have suggested that thrombopoiesis may occur in the lungs. To investigate the role of the lungs in platelet production, we measured automated platelet parameters in blood from the pulmonary artery and the radial artery ($n = 125$) or aorta ($n = 26$) in patients undergoing aorto-coronary bypass. No significant differences were found between pulmonary and radial arterial blood with regard to platelet count (192.132 ± 46.250 *vs.* $192.004 \pm 46.294 \times 10^9$/l), mean platelet volume (11.03 ± 1.04 *vs.* 11.03 ± 1.03 fl), plateletcrit (0.212 ± 0.051 *vs.* $0.212 \pm 0.051 \times 10^{-2}$), platelet distribution width (14.48 ± 2.16 *vs.* 14.47 ± 2.08 fl) and platelet–large cell ratio (0.350 ± 0.076 *vs.* 0.351 ± 0.078). Similar results were obtained in comparisons between pulmonary arterial and aortic blood. A coefficient of linear correlation of 0.98 was found between the pulmonary and radial arterial and aortic platelet counts. These findings suggest that the platelet population entering the lungs was the same as the platelet population leaving them. Our results do not therefore support the theory of pulmonary platelet production.

Keywords Platelet production, lungs, arterial platelet counts, aortic platelet counts

Introduction

Since Aschoff (1893) described the presence of megakaryocytes in the lungs, the site of platelet production has been a subject of debate. Howell and Donahue (1937) reported a higher platelet count in blood leaving the lungs than in blood entering them and suggested that megakaryocytes concentrated in the lungs contribute actively to platelet production. This view, supported by Bierman (1955), Sharnoff and Scardino (1960) and Tinggaard Pedersen (1974), was challenged by Jordan (1940) and by Fidlar and Waters (1941).

Numerous authors have confirmed the presence of megakaryocytes in circulating blood, in the lungs and in many locations other than the bone marrow, both in human subjects and in experimental animals (Oelhafen, 1914; Kaufman *et al.*, 1965a; Tinggaard Pedersen, 1974 and 1978, Hansen & Tinggaarden Pedersen, 1978; Levine *et al.*, 1993). It is therefore widely accepted that megakaryocytes migrate through the marrow–blood barrier to enter the circulation (Tavassoli & Aoki, 1981). The great number found in the lungs has been ascribed to filtration in the pulmonary capillary bed (Tinggaard Pedersen, 1974 and 1978, Trowbridge, Martin & Slater, 1982; Levine *et al.*, 1993). Since the work of Wright (1906), the megakaryocyte cytoplasm has been recognized as the source of platelet production. It has been observed that circulating megakaryocytes are fewer in number and their cytoplasm poor or absent after their passage through the lungs (Tinggaard Pedersen, 1974 and 1978; Levine *et al.*, 1993). As bare megakaryocyte nuclei are not commonly noted in normal marrow, it has been suggested that the pulmonary capillaries are the sole site (Trowbridge *et al.*, 1982; Slater, Trowbridge & Martin, 1983) or the primary site (Levine *et al.*, 1993) of platelet production. Others have estimated that proportions of the platelet mass ranging from 7 to 17% to 33% are released in the pulmonary capillaries (Kaufman *et al.*, 1965b).

Accepted for publication 31 January 2002
Correspondence: Prof. Giuseppe Aliberti, Dipartimento di Scienze Cliniche, Policlinico Umberto I, Viale del Policlinico, 00161 Roma, Italy. Fax: + 39 6 49970524; E-mail: giuseppe.aliberti@uniroma1.it

To investigate the role of the lungs in the process of platelet production, we measured automated platelet parameters in blood from the pulmonary and radial arteries and the aorta in humans.

Patients and methods

The study was carried out, after obtaining informed consent, in patients undergoing aorto-coronary bypass for atherosclerotic coronary disease. All patients were operated upon using the same anaesthetic and surgical techniques. After sternotomy and before heparin anticoagulation, hypothermia and extracorporeal circulation were performed, arterial blood specimens were drawn almost simultaneously into sterile syringes. These were taken from the pulmonary and radial arteries in 125 patients (111 men and 14 women, mean age 61.79 ± 8.67 years) and from the pulmonary artery and aorta in 26 patients (23 men and 3 women, mean age 61.68 ± 7.74 years). The blood samples were transferred immediately after collection into K_3EDTA anticoagulated vacutainer tubes (Becton-Dickinson, Plymouth, UK). Automated platelet parameters were measured within two hours of collection, using a Sysmex^{TM} NE-8000 device (TOA Medical Electronics CO., Kobe, Japan), employing the electrical impedence principle. Platelet particle size distribution analysis was performed by a lower discriminator, set automatically in the size range between 2 and 6 fl, an upper discriminator, set automatically in the range between 12 and 30 fl, and a fixed discriminator set at 12 fl.

The parameters measured were: platelet count (PLT), mean platelet volume (MPV), plateletcrit (Pct), platelet distribution width (PDW) (measured at the 20% level taking the histogram peak as 100%) and platelet-large cell ratio (P-LCR). P-LCR was obtained by dividing the number of cells included in the range between the fixed and the upper discriminator by the total number of cells counted between the lower and the upper discriminator (PLT). The haematocrit (Hct) was measured in all samples to avoid spurious results due to differences in composition of blood from the pulmonary and radial arteries. The intra-assay and interassay coefficients of variation were 6% in the range of the study and each value was the mean of duplicate assays. Student's paired *t*-test was used for statistical analysis (Statistica software, Statsoft, Inc, Tulsa, Oklahoma, USA, 1993).

Results

There were no differences in the platelet parameters between pulmonary and radial arterial blood (Table 1). Hct values were significantly higher in pulmonary than in radial arterial blood ($P < 0.0005$). Coefficients of inverse linear correlation between PLT and MPV were −0.25 in pulmonary arterial blood ($P < 0.01$) and −0.24 in radial arterial blood ($P < 0.01$). A very high positive linear correlation was found between the pulmonary arterial and radial arterial PLT ($r = 0.98$, $P < 0.001$), MPV ($r = 0.97$, $P < 0.001$), Pct ($r = 0.98$, $P < 0.001$), PDW ($r = 0.96$, $P < 0.001$) and P-LCR ($r = 0.98$, $P < 0.001$).

Similar results were obtained in comparisons between pulmonary arterial and aortic blood. No significant differences were found with respect to PLT (175.326 ± 51.233 *vs.* 175.096 ± 50.301 10^9/l, NS), MPV (10.90 ± 0.71 *vs.* 10.88 ± 0.70 fl, NS), PDW (13.74 ± 1.27 *vs.* 13.66 ± 1.33 fl, NS) and P-LCR (0.332 ± 0.054 *vs.* 0.337 ± 0.056, NS). Coefficients of linear correlation were 0.99 for PLT ($P < 0.001$), 0.98 for MPV ($P < 0.001$), 0.95 for PDW ($P < 0.001$) and 0.97 for P-LCR ($P < 0.001$).

Table 1. Values of the platelet parameters and of the haematocrit ± SD in blood from the pulmonary and the radial arteries ($n = 125$)

	Pulmonary artery	Radial artery	MD	*P* levels
PLT (10^9/l)	192.132 ± 46.250 (183.944–200.319)	192.004 ± 46.294 (183.808–200.199)	0.128 ± 8.024	0.86
MPV (fl)	11.03 ± 1.04 (10.84–11.20)	11.03 ± 1.03 (10.85–11.21)	0.008 ± 0.239	0.69
Pct (10^{-2})	0.212 ± 0.051 (0.202–0.221)	0.212 ± 0.051 (0.203–0.221)	0.002 ± 0.091	0.81
PDW (fl)	14.48 ± 2.16 (14.10–14.87)	14.47 ± 2.08 (14.10–14.84)	0.14 ± 0.60	0.79
P-LCR (1)	0.350 ± 0.076 (0.335–0.364)	0.351 ± 0.078 (0.336–0.366)	0.0015 ± 0.016	0.33
Hct (1)	0.366 ± 0.041 (0.357–0.374)	0.364 ± 0.040 (0.355–0.372)	0.0021 ± 0.0050	0.00015

MD, mean difference ± SD; 95% confidence intervals in brackets.

Discussion

Since the report of Howell and Donahue (1937), several groups have insisted that the lungs are the sole source or the main source of platelet production. The present study, carried out in a substantial number of subjects, on blood drawn directly from the pulmonary and radial arteries and the aorta showed no differences in platelet parameters between blood entering the lungs and blood leaving them. The PLT was in fact slightly lower in arterial blood, due possibly to the respiratory change in haematocrit. A similar, insignificant difference has been observed between peripheral venous and arterial blood in a small number of subjects (Aliberti *et al*., 1996).

If substantial thrombopoietic activity occurred in the lungs, a higher steady state PLT would be expected in radial arterial than in pulmonary arterial blood, resulting from pooling of pulmonary and systemic platelet production. This has been reported in cats, rabbits and rats by a number of authors (Howell & Donahue, 1937; Sharnoff & Scardino, 1960; Tinggaard Pedersen, 1974). While similar results have been reported in humans (Howell & Donahue, 1937; Bierman, 1955), these studies employed unphysiological experimental models (Jordan, 1940), imprecise counting methods, and, in some cases, unreliable statistical analyses. There are numerous reports of arterio-venous differences in megakaryocyte counts and morphology, presented as further evidence of pulmonary platelet production. These studies have demonstrated higher counts of intact, megakaryocytes in central venous blood, with fewer megakaryocytes in aortic, arterial and peripheral venous blood, many with scanty cytoplasm or naked nuclei (Kaufman *et al*., 1965a and 1965b; Tinggaard Pedersen, 1978; Trowbridge *et al*., 1982; Slater *et al*., 1983; Levine *et al*., 1993). It has been suggested that these differences were due to the filtration of megakaryocytes in the lungs and subsequent fragmentation of their cytoplasm to form platelets.

Although the presence of megakaryocytes in circulating blood is accepted as a normal finding, our results do not support this view. Not only was no difference found between pulmonary arterial, radial arterial and aortic blood with respect to PLT, but MPV, P-LCR, PDW (an index of platelet size heterogeneity) and Pct were also identical. A similar inverse correlation was observed between PLT and MPV in the pulmonary and systemic circulations. This has been observed in humans and in several mammalian species (Nakeff & Ingram, 1970; O'Brien & Jamieson, 1974), and has been interpreted as evidence of a homeostatic mechanism regulating platelet production. Moreover, very high coefficients of positive linear correlation were found between the pulmonary arterial, radial arterial and aortic platelet parameters, especially for PLT ($r = 0.98$). This suggests that the platelet population entering the lungs was the same as the population leaving. This should not occur if there were random fragmentation of megakaryocyte cytoplasm in the pulmonary capillaries, with platelet release.

In conclusion, the present study does not support the theory that significant platelet production occurs in the lungs, as the platelet population is identical before and after pulmonary passage.

References

Aliberti G., Proietta M., Pulignano I. & De Franceschi L. (1996) Differences in platelet count and size between marrow and peripheral blood. *Haemostasis* **26,** 276–283.

Aschoff L. (1893) Uber capillare embolie von riesenkernhaltigen zellen. *Archiv Fur Pathologhische Anatomie und Physiologie* **134,** 11–26.

Bierman H.R. (1955) The hematologic role of the lung in man. *American Journal of Surgery* **89,** 130–140.

Fidlar E. & Waters E.T. (1941) The origin of platelets. Their behavior in the heart-lung preparation. *Journal of Experimental Medicine* **73,** 299–307.

Hansen M. & Tinggaarden Pedersen N. (1978) Circulating megakaryocytes in blood from the antecubital vein in healthy, adult humans. *Scandinavian Journal of Haematology* **20,** 371–376.

Howell W.H. & Donahue D.D. (1937) The production of blood platelets in the lungs. *Journal of Experimental Medicine* **65,** 177–203.

Jordan H.E. (1940) The origin and significance of the megakaryocytes of the lungs. *Anatomical Record* **77,** 91–100.

Kaufman R.M., Airo R., Pollack S. & Crosby W.H. (1965b) Circulating megakaryocytes and platelet release in the lung. *Blood* **26,** 720–729.

Kaufman R.M., Airo R., Pollack S., Crosby W.H. & Doberneck R. (1965a) Origin of pulmonary megakaryocytes. *Blood* **25,** 767–774.

Levine R.F., Eldor A., Shoff P.K., Kirwin S., Tenza D. & Cramer E.M. (1993) Circulating megakaryocytes: Delivery of large numbers of intact, mature megakaryocytes to the lungs. *European Journal of Haematology* **51,** 233–246.

Nakeff A. & Ingram M. (1970) Platelet count: volume relationship in four mammalian species. *Journal of Applied Physiology* **28,** 530–533.

O'Brien J.R. & Jamieson S. (1974) A relationship between platelet volume and platelet number. *Thrombosis and Diathesis Haemorrhagica* **31,** 363–365.

Oelhafen H. (1914) Uber knochenmarkriesen zellen im stromenden blut. *Folia Haematologica* **18,** 171–181.

Sharnoff J.G. & Scardino V. (1960) Platelet-count differences in blood of the rabbit right and left heart ventricles. *Nature* **187,** 334–335.

Slater D.N., Trowbridge E.A. & Martin J.F. (1983) The megakaryocyte in thrombocytopenia: a microscopic study which supports the theory that platelets are produced in the pulmonary circulation. *Thrombosis Research* **31,** 163–176.

Tavassoli M. & Aoki M. (1981) Migration of entire megakaryocytes through the marrow–blood barrier. *British Journal of Haematology* **48,** 25–29.

Tinggaard Pedersen N. (1974) The pulmonary vessels as a filter for circulating megakaryocytes in rats. *Scandinavian Journal of Haematology* **13,** 225–231.

Tinggaard Pedersen N. (1978) Occurrence of megakaryocytes in various vessels and their retention in the pulmonary capillaries in man. *Scandinavian Journal of Haematology* **21,** 369–375.

Trowbridge E.A., Martin J.F. & Slater D.N. (1982) Evidence for a theory of physical fragmentation of megakaryocytes, implying that all platelet are produced in the pulmonary circulation. *Thrombosis Research* **28,** 461–475.

Wright J.H. (1906) The origin and nature of the blood plates. *Boston Medical and Surgical Journal* **154,** 643–645.