Pulmonary megakaryocytes: "missing link" between cardiovascular and respiratory disease?

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SUMMARY Pulmonary megakaryocytes were quantitated in a series of 30 consecutive hospital necropsies using a two stage immunoperoxidase stain for factor VIII related antigen. In all 30 cases they were found with a mean density of 14.65 megakaryocytes/cm² in lung sections of 5 µm in thickness. The maximum concentration of intrapulmonary megakaryocytes was consistently found to be in the central zone of the right upper lobe. Less than 22% of the observed cells possessed abundant cytoplasm, the rest appearing as effete, naked, and seminaked nuclei. The mean megakaryocyte count was found to be increased in association with both respiratory pathology (positive smoking history and impaired lung function) and cardiovascular disease states—shock; thromboembolism; myocardial infarction; and severe atheroma in the abdominal aorta, the coronary circulation, and the circle of Willis. Pulmonary megakaryocytes probably embolise from bone marrow. This may reflect stimulated thrombopoiesis, caused by increased platelet consumption in association with atherosclerotic disease, but it cannot be taken to confirm that the lung is the principal site of platelet production.

The megakaryocyte is now firmly established as the source of all platelets, but the exact site and mechanisms of platelet production and release remain in doubt.1 It is widely accepted that nascent platelets are delineated within the megakaryocyte cytoplasm by a demarcation membrane system2 which forms by invagination of the plasmalemma.3 This provides the lines of cleavage and will ultimately form the platelet plasma membrane. The actual release of platelets into the circulation is explained by the "pseudopodial theory"4-8 which proposes that a megakaryocyte produces about six elongated cytoplasmic pseudopodia, each with a core of platelet organelles. These pro-platelets penetrate the vascular sinusoids via the transendothelial route and, after being pinched off into the bloodstream, eventually fragment to yield about 1000 platelets. Recently, however, it was suggested that all platelet production occurs in the pulmonary microvasculature by the physical fragmentation of megakaryocyte emboli9 10 and considerable evidence supports this theory:

1 The migration of intact megakaryocytes across the marrow-blood barrier has been confirmed by both static ultrastructural9 11 and dynamic microcinematographic studies.12

2 Intact megakaryocytes are now known to be normal constituents of blood.13

3 Intrapulmonary megakaryocytes are a consistent finding at necropsy,14 especially in disease states15 and, despite early conflict of opinion,16 17 vascular rearrangement experiments have proved that they do not arise de novo but are brought to the lungs by the venous blood.18

4 The lungs serve as a filter for circulating megakaryocytes because there is a reduction in both the number and size of megakaryocytes as blood flows through the pulmonary microcirculation.19-24

5 Platelet production in the lungs is indicated by higher platelet counts in central arterial blood than in central venous blood.16 22 23

The above evidence indicates that pulmonary megakaryocytes are emboli from the marrow, which, due to their large size, are retained and fragmented in the intrapulmonary capillaries to yield platelets. Agreement has not been reached, however, on the extent of their contribution to the total platelet population, with values from 7%25 to almost 100%21 being reported. Recently, the platelet volume distribution, as measured by particle sizing, was shown to be log normal rather than the Gaussian distribution usually shown by mitotic cells.26 It has been suggested that this unique volume distribution can be
explained only if all platelet production occurs in the lungs by a process of physical fragmentation, probably as a result of sequential random binary divisions at the pulmonary bifurcations. If this is the case then disturbance of pulmonary-megakaryocyte interaction may cause dysthrombopoiesis, which, in turn, may explain the common coexistence of cardiovascular and respiratory disease.

This study aimed to explore these possibilities by investigating the incidence, concentration, distribution, and morphology of pulmonary megakaryocytes in a series of hospital necropsies and relating the findings to respiratory and atherothrombotic disorders.

**Material and methods**

A block of tissue 1–2 cm² x 0–5 cm was collected from the centre and periphery of each of the four main lung lobes during 30 consecutive unselected hospital post mortem examinations at the Leicester Royal Infirmary. Care was taken to avoid areas with large airways or obvious evidence of disease. After overnight fixation in 5% formol/acetic acid (5% glacial acetic acid in 4% neutral phosphate buffered formaldehyde solution) the tissue was paraffin processed and cut into 5 μm sections. These were then stained for factor VIII related antigen, using an indirect immunoperoxidase technique, as described by Crocker and Smith. Factor VIII related antigen is found on the platelet membrane, some of it being adsorbed on to receptors from the plasma but a high proportion being an integral part of the platelet membrane and originating from the demarcation membrane system.

The area of each section was determined by planimetry using a Kontron Videoplan with graphic tablet before screening for megakaryocytes with a Leitz SM-Lux microscope, using the x 40 objective; all suspect cells were examined under oil immersion, using the x 100 objective. Megakaryocytes were categorised into three types: intact nuclei; seminaked nuclei; and naked nuclei (fig 1). A fourth category, the "possible", or "?" megakaryocyte, was also used to include cells satisfying some but not all the criteria needed for the above three forms. Cells resembling

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**Fig 1** Morphology of intrapulmonary megakaryocytes.

**Fig 1a** Intact megakaryocyte is large intravascular cell with large multilobed hyperchromatic nucleus enclosed by abundant positively staining cytoplasm.

**Fig 1b** Seminaked megakaryocyte nucleus is similar but smaller due to loss of cytoplasm.

**Fig 1c** Naked megakaryocyte nucleus is large intensely staining nucleus, totally denuded of cytoplasm, and moulded into shape of enclosing vascular channel.

(DAB staining of peroxidase-antiperoxidase preparations.) All magnifications x 320.
megakaryocytes were occasionally seen in the extra-
vascular spaces. These could be either true me-
gakaryocytes or large alveolar macrophages and so were
included in the "?" category. After attending the
necropsy and studying the clinical case notes three
sets of clinicopathological data were recorded.

RESPIRATORY SYSTEM
The subjects were divided into smokers and non-
smokers, and pulmonary performance was classified
as normal or impaired according to the clinical his-
tory, physical signs, and lung function tests (if per-
formed).

<table>
<thead>
<tr>
<th>Site of tissue sampling</th>
<th>No of megakaryocytes/cm²</th>
<th>Absolute difference (1-2)</th>
<th>(% ) difference (1-2)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right lung</td>
<td>15-58</td>
<td>13-69</td>
<td>1-89</td>
<td>8-27</td>
</tr>
<tr>
<td>Upper lobes</td>
<td>15-67</td>
<td>14-34</td>
<td>1-33</td>
<td>6-37</td>
</tr>
<tr>
<td>Central zones</td>
<td>16-41</td>
<td>14-57</td>
<td>1-84</td>
<td>6-66</td>
</tr>
</tbody>
</table>

Table 1 Intrapulmonary distribution of megakaryocytes (mean values for 30 subjects)

CARDIOVASCULAR SYSTEM
Shock Shock was diagnosed from a clinical descrip-
tion of pallor, sweating, tachycardia, and hypo-
tension (100/70 mm Hg being taken as an arbitrary
lower limit for the normal blood pressure) at some
stage during the week before death.
Thromboembolism The presence or absence of
thromboembolic disease was determined solely from
the necropsy findings. Myocardial infarction Infarcts found at necropsy
were described as being small (less than 1 cm²),
medium (1–3 cm²), or large (greater than 3 cm² or
transmural).

<table>
<thead>
<tr>
<th>Disease</th>
<th>No of subjects</th>
<th>Mean</th>
<th>Range</th>
<th>Standard deviation</th>
<th>p value</th>
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<tbody>
<tr>
<td>Smoking history</td>
<td>Non-smoker</td>
<td>14</td>
<td>12-96</td>
<td>3-59–36-71</td>
<td>7.39</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal</td>
<td>7</td>
<td>13-53</td>
<td>1-71–21-00</td>
<td>6-23</td>
</tr>
<tr>
<td></td>
<td>Impaired</td>
<td>22</td>
<td>15-57</td>
<td>3-59–36-71</td>
<td>7.90</td>
</tr>
<tr>
<td>Shock</td>
<td>Absent</td>
<td>23</td>
<td>12-97</td>
<td>1-71–29-66</td>
<td>7.17</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>7</td>
<td>20-12</td>
<td>12-15–36-71</td>
<td>7.40</td>
</tr>
<tr>
<td>Thromboembolic disease</td>
<td>Absent</td>
<td>16</td>
<td>13-22</td>
<td>1-71–29-66</td>
<td>7.65</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>14</td>
<td>16-25</td>
<td>3-78–36-71</td>
<td>7.72</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Absent</td>
<td>23</td>
<td>13-24</td>
<td>1-71–29-66</td>
<td>7.00</td>
</tr>
<tr>
<td></td>
<td>Small</td>
<td>1</td>
<td>36-71</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>1</td>
<td>18-20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>3</td>
<td>16-35</td>
<td>12-15–22-19</td>
<td>4.25</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>21</td>
<td>14-96</td>
<td>4-01–29-66</td>
<td>6.53</td>
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<tr>
<td></td>
<td>Female</td>
<td>9</td>
<td>12-33</td>
<td>1-71–36-71</td>
<td>10-90</td>
</tr>
<tr>
<td>Infection</td>
<td>Absent</td>
<td>15</td>
<td>15-00</td>
<td>1-71–36-71</td>
<td>8.85</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>12</td>
<td>13-93</td>
<td>4-01–29-66</td>
<td>7.25</td>
</tr>
<tr>
<td>Blood-borne</td>
<td>Absent</td>
<td>3</td>
<td>15-60</td>
<td>13-17–19-53</td>
<td>2.81</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Absent</td>
<td>16</td>
<td>15-80</td>
<td>1-71–36-71</td>
<td>8.96</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>6</td>
<td>12-29</td>
<td>3-78–23-32</td>
<td>7.64</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Absent</td>
<td>8</td>
<td>14-07</td>
<td>6-95–19-53</td>
<td>4.30</td>
</tr>
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</table>

Table 2 Pulmonary megakaryocyte counts related to various clinicopathological data

<table>
<thead>
<tr>
<th>Clinicopathological information</th>
<th>Megakaryocytes/cm² in sections of lung</th>
<th>No of subjects</th>
<th>Mean</th>
<th>Range</th>
<th>Standard deviation</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>Haemoglobin</td>
<td>Normal</td>
<td>12</td>
<td>17-01</td>
<td>3-59–36-71</td>
<td>9.42</td>
<td>p = 0.03</td>
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<tr>
<td></td>
<td>M = 16 ± 2 g/dl</td>
<td>16</td>
<td>14-35</td>
<td>4-01–22-46</td>
<td>5.83</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td></td>
<td>F = 14 ± 2 g/dl</td>
<td>7</td>
<td>20-38</td>
<td>14-72–36-71</td>
<td>7.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>7</td>
<td>20-38</td>
<td>14-72–36-71</td>
<td>7.53</td>
<td></td>
</tr>
<tr>
<td>White cell count</td>
<td>Normal</td>
<td>20</td>
<td>14-01</td>
<td>3-95–29-66</td>
<td>7.11</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>7 ± 3 x 10³/l</td>
<td>20</td>
<td>14-01</td>
<td>3-95–29-66</td>
<td>7.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>7</td>
<td>13-85</td>
<td>4-01–22-46</td>
<td>5.91</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Normal</td>
<td>17</td>
<td>16-98</td>
<td>6-95–22-19</td>
<td>6.99</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td></td>
<td>290 ± 150 x 10⁹/l</td>
<td>4</td>
<td>11-98</td>
<td>6-95–22-19</td>
<td>6.99</td>
<td>p &gt; 0.1</td>
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<tr>
<td></td>
<td>Low</td>
<td>7</td>
<td>13-85</td>
<td>4-01–22-46</td>
<td>5.91</td>
<td>p &gt; 0.1</td>
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<tr>
<td>Fever</td>
<td>Absent</td>
<td>12</td>
<td>16-84</td>
<td>3-59–36-71</td>
<td>8.62</td>
<td>p &gt; 0.1</td>
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<td></td>
<td>Present</td>
<td>17</td>
<td>14-27</td>
<td>4-01–29-66</td>
<td>7.02</td>
<td>p &gt; 0.1</td>
</tr>
</tbody>
</table>
Aortic atheroma The abdominal aorta was opened longitudinally and atheromatous severity was assessed, as described by McGill et al., by comparing it with a panel of aortas graded 1–2 to 6–7 inclusive. Four of the 30 cases studied could not be satisfactorily equated with any of the six specimen aortas; two were designated as grade 1 atheroma while the other pair (both from newborn babies) were classified as grade 0 atheroma.

Coronary atheroma The main coronary arteries were cut transversely at regular intervals and the luminal diameter assessed. Four grades of atheromatous severity were recognised: absent or all main coronary vessels widely patent; mild, or minimal luminal narrowing of one of the major arteries; moderate or less than 50% luminal reduction of one or more of the major coronary arteries; severe, or greater than 50% reduction of the luminal diameter of all three main coronary arteries.

Cerebral atheroma Atherosclerotic disease in the circle of Willis was absent (widely patent), mild (noticeable luminal reduction), or severe (lumen more than 50% occluded).

**Results**

**THE INCIDENCE AND CONCENTRATION OF PULMONARY MEGAKARYOCYTES**

Megakaryocytes were found in the lungs of all 30 necropsy specimens studied, but their concentration was variable, ranging from only 2 megakaryocytes/cm² to as many as 37 megakaryocytes/cm² (mean 14.65 megakaryocytes/cm²).

**Fig 2** Pulmonary megakaryocyte counts and aortic atheroma.

**Fig 3** Pulmonary megakaryocyte counts and coronary atheroma.

**MISCELLANEOUS VALUES**

The following miscellaneous clinicopathological data were also recorded: sex, age, infection (absent, present, or blood borne), malignancy (absent, present, or metastatic), and the antemortem haemoglobin, white cell count, platelet count, and body temperature.
"Missing link" between cardiovascular and respiratory disease

The incidence of pulmonary megakaryocytes was 100%, thereby supporting the results of previous work. This seems to be correlated with the general condition of patients before they die. One other study reported pulmonary megakaryocytes in 95% of hospital necropsies but only 67% of forensic necropsies.

The concentration of pulmonary megakaryocytes (14-65 megakaryocytes/cm² in 5 μm sections) coincides closely with the results of Smith and Butcher, who counted 100 high power fields and reported mean values of 14-2 megakaryocytes/mm³ for their hospital cases but only 5-1 megakaryocytes/mm³ for their forensic series. Aabo et al., however, quote an average of 4 megakaryocytes/cm² in forensic necropsies and 37 megakaryocytes/cm² in hospital necropsies in 7 μm lung sections and estimate the maximum density in normal lungs to be 18 megakaryocytes/cm².

More recently, a study of burns victims found less than 2 megakaryocytes/cm² in lung sections of unspecified thickness. There are two possible reasons for this variation in the reported concentration of pulmonary megakaryocytes. Firstly, the pulmonary megakaryocyte count may be greater in hospital deaths than in forensic cases due to an effect of disease states such as acute infections, leucocytosis, haemorrhage, postoperative states, shock, and the adult respiratory distress syndrome. Consumptive coagulopathy is believed to be the common pathogenetic mechanism producing increased pulmonary megakaryocyte counts in these states. Secondly, previous studies have relied entirely on morphology for the identification of megakaryocytes in sections stained with haematoxylin and eosin or periodic acid Schiff. Wells et al. explained their low pulmonary megakaryocyte counts by their use of more stringent criteria to define a megakaryocyte. In this respect our investigation more reliably indicates the intrapulmonary megakaryocyte density, because it not only uses an immunocytochemical stain to assist in identification, but it also clearly defines the morphological criteria needed to identify a megakaryocyte.

The distribution of megakaryocytes is not uniform, and there is an appreciably greater concentration of cells in the right lung than in the left. This contrasts with the results of previous work, and there is no obvious explanation. It could be a simple "pooling effect"; perhaps right handed subjects are more likely to lie on their right side. The right lung may receive a disproportionately greater share of the cardiac output, or, because of the phenomenon of "plasma skimming", the left pulmonary artery, which arises as an

THE INTRAPULMONARY DISTRIBUTION OF MEGAKARYOCYTES

Table 1 shows that there is a higher concentration of megakaryocytes in the right lung than in the left, in the upper lobes than in the lower lobes, and in the central zones than in the periphery.

THE MORPHOLOGY OF PULMONARY MEGAKARYOCYTES

In all parts of the lungs only 22% of megakaryocytes were intact, with copious cytoplasm. Thirty one per cent were seminaked nuclei, 31% were naked nuclei, and the remaining 16% were classed "?"

PULMONARY MEGAKARYOCYTES AND CLINICOPATHOLOGICAL RELATIONS

Respiratory system Pulmonary megakaryocytes were slightly increased in association with both a positive smoking history and impaired respiratory function, though significance was reached only in the case of a positive smoking history (table 2).

Cardiovascular system There was a significant increase in the pulmonary megakaryocyte count in association with shock, myocardial infarction, and severe atheroma in the abdominal aorta, coronary circulation, and the cerebral vessels. The increase in pulmonary megakaryocytes in thromboembolic disease was only slight (table 2 and figs 2, 3, and 4).

Miscellaneous clinicopathological data The pulmonary megakaryocyte count was significantly higher in relation to leucocytosis and slightly higher in men than in women, but there was no obvious association with age, infection, neoplasia, haemoglobin concentration, platelet count, or fever (table 2).

Discussion

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offshoot from the main trunk, may receive only dilute plasma. Unknown local factors may make megakaryocyte filtration more effective or fragmentation less efficient in the right lung, or both.

The upper lobes have a consistently greater megakaryocyte count than the lower lobes, thus supporting the conclusions of Bendix-Hansen et al., who explained this in terms of bed rest changing the pulmonary blood flow. Our observations also showed that pneumatic consolidation was mostly confined to the lower lobes whereas emphysematous changes were almost exclusive to the upper lobes.

Emphysema may either cause an actual increase in intrapulmonary megakaryocytes or simply facilitate their identification; the converse is true for pneumonia. These two factors may be interrelated as severe basal congestion tends to divert blood to the upper lobes.

Consistent with the findings of previous work, the central zones have a greater megakaryocyte count than the lung periphery. Again, differential blood flow is a likely explanation, although the greater degree of expansion and contraction undergone by peripheral lung tissue may also be important factors.

**PULMONARY MEGAKARYOCYTES AND RESPIRATORY AND CARDIOVASCULAR PATHOLOGY**

The common coexistence of pulmonary and atherothrombotic disorders is well known and cigarette smoking has been implicated in both chronic bronchitis and coronary artery disease. The causal factors in these disorders often coexist — cigarette smokers are more likely to consume a high fat diet — these being established risk factors in respiratory and cardiovascular pathology, respectively. When Friedman et al. failed to account for their observed association between diminished vital capacity and clinical coronary artery disease in terms of these accepted explanations, they suggested the existence of “some other connection between pulmonary function and the state of the coronary arteries or myocardium.”

There are three such possibilities: firstly, chronic respiratory disease may cause hypoxia which increases aortic cholesterol accumulation, probably due to ischaemic endothelial injury; secondly, lung disease may impair intrapulmonary production of prostacyclin production, thereby disturbing the normal arterial homeostasis between prostacyclin and thromboxane $A_2$, and thus predisposing to atherothrombosis; thirdly, if pulmonary megakaryocytes are the principal source of platelets then disturbance of the lung and megakaryocyte interaction (due to a change in either the pulmonary vessels and their biochemical environment or in the megakaryocyte size and protein structure) may result in dysthrombopoiesis and thus predispose to both respiratory and cardiovascular disease. Our results indicate an increased pulmonary megakaryocyte count in association with both respiratory disease and cardiovascular disease, especially shock and thromboembolism (both findings agree with those of previous reports). Myocardial infarction, and severe atheroma.

There are two explanations for these observations. Firstly, the number of pulmonary megakaryocytes may be increased in association with respiratory disease, with resulting secondary atherothrombotic complications. It has already been shown that the efficiency of the pulmonary vascular filter can be affected by lung diseases such as bronchitis and bronchopneumonia. Impaired megakaryocyte fragmentation in certain respiratory disorders may yield larger fragments than usual — some of these may be retained in the lungs and appear as naked or seminaked nuclei, while others will escape into the peripheral circulation. As large platelets may be more reactive, this would predispose to secondary atherothrombosis. Supporting evidence comes from reports of an increased mean platelet volume in relation to both chronic hypoxia and myocardial infarction.

Interestingly, only 22% of the megakaryocytes that we observed in the lungs possessed copious cytoplasm, thereby suggesting that most are either released from the marrow as effete naked or seminaked nuclei, or that intact cells embolising through the lungs are rapidly fragmented in the pulmonary capillaries. This explanation seems unlikely, however, as the relative proportion of naked and seminaked megakaryocyte nuclei in patients with severe atheroma was not increased. A more likely association is that the number of pulmonary megakaryocytes is increased in association with atherosclerotic disease because of enhanced thrombopoiesis due to increased platelet consumption — either as a result of a genetically or environmentally acquired tendency, or both, to increased platelet-vessel wall interaction, or as a result of increased platelet adherence to ulcerated atheroma. Respiratory complications may subsequently develop as a direct consequence of the increased presence and fragmentation of megakaryocytes in the lungs, a feature already implicated in asthma, pulmonary hypertension, the shock lung and the adult respiratory distress syndrome.

The higher pulmonary megakaryocyte counts found in men are consistent with a higher incidence of pulmonary and cardiovascular disease also found in men. The failure to show a correlation between the megakaryocyte counts before and after death, although consistent with that of previous reports, is not consistent with the hypothesis that the lungs are the principal site of thrombopoiesis. The pulmonary
megakaryocyte content may be disturbed by the circulatory changes associated with death, a view supported by the fact that there is a direct relation between the circulating platelet count in life and the pulmonary megakaryocyte density; the introduction of thrombocytopenia in experimental animals increases both circulating and intrapulmonary megakaryocytes. Previous reports indicate that the pulmonary megakaryocyte density is affected by both haemorrhage and hypoxia. Our findings in relation to shock agree with this. There was no relation, however, between the megakaryocyte numbers in the lungs and the haemoglobin concentration.

In contrast to the findings of previous work, we found no appreciable increase in the pulmonary megakaryocyte count in association with fever, infection, or neoplasia, though leucocytosis did have a positive effect. Similarly, despite increasing atheromatous disease with advancing age there was no demonstrable increase in the pulmonary megakaryocyte count. This, however, probably reflects age clustering, as most of the subjects were of late middle age (mean age = 59-2 years, (SD 22-33)). Our findings suggest that, although the lungs may not be the major site of platelet production, it would be wise not to neglect the role of pulmonary megakaryocytes in thrombopoiesis, particularly in relation to cardiovascular and pulmonary diseases.

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References


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