The Release of Leukocytes and Platelets from the Pulmonary Circulation by Epinephrine


The intravenous administration of epinephrine is usually associated with a prompt leukocytosis and thrombocytosis which has often been attributed to delivery of these elements into the circulation from the spleen. A number of observations, however, are contradictory to this premise. First, the leukocytosis following epinephrine administration has been observed after splenectomy. Secondly, the leukocyte increases observed peripherally cannot always be accounted for solely by the number of cells leaving the splenic vein. Thirdly, the splenic artery exhibits almost complete spasm which persists for 1 to 2 minutes following the administration of epinephrine into this artery. It has also been shown that the release of additional cells from the spleen does not become apparent for 2 to 4 minutes after epinephrine administration while the peripheral arterial blood exhibits an immediate leukocytosis.

The pulmonary circulation has a prodigious capacity for both withdrawal and delivery of leukocytes from and into blood. The lungs also are capable of both removing and adding cells to the circulating blood during inspiration and expiration, respectively, while maintaining the mean level relatively constant. The sequestration of leukocytes in the pulmonary circulation under such varying circumstances strongly suggests that the lungs may be a potential reservoir for formed elements which can be rapidly released into circulation. Howell and Donahue believed the lungs were a source of platelets in the dog but their work has not been confirmed. The lungs in the rabbit, dog and man are an excellent source of thromboplastin-like activity which is a major component of the platelet. Accordingly, the pulmonary circulation was investigated with particular regard to changes in number of the circulating leukocytes and platelets following the intravenous administration of epinephrine.

Subjects and Methods

Twelve patients with neoplastic diseases were selected for this study primarily because of their relatively good cardiopulmonary status. Venous blood was obtained from the right ventricle or pulmonary artery by intracardiac catheterization in 9 patients and from a large basilic vein via an indwelling large-bore venous needle in the remaining 3 patients. Arterial blood was obtained simultaneously from a large peripheral artery via a large bore indwelling needle.

Epinephrine in concentrations of 0.1 to 0.3 mg. in saline was administered at a uniform rate over a 30 to 60 second period. L-epinephrine and norepinephrine in isotonic solution...
<table>
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<th>Name</th>
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<th>Sex</th>
<th>Diagnosis</th>
<th>Dose</th>
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<th>Initial Leukocyte Rise</th>
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<th>Control Platelet Count</th>
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<td>2,600</td>
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<td></td>
<td></td>
<td>7,800</td>
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<td>+13</td>
<td>190,000</td>
<td>365,000</td>
<td>+142</td>
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**Remarks on Leukocytes**

- Arterial rise preceded the venous rise and was higher
- Arterial rise preceded the venous rise and was higher
- Arterial rise preceded the venous rise and was higher
- Arterial rise preceded the venous rise and was higher
- Arterial rise preceded the venous rise and was higher
- Arterial rise preceded venous rise and was higher
- Arterial rise preceded the venous rise and was higher, but the rise was slight and the count below 2500
- Arterial rise preceded the venous rise and was higher
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<th>Artery at 60 sec</th>
<th>Venous at 60 sec</th>
<th>Artery at 180 sec</th>
<th>Venous at 180 sec</th>
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<td>17,100</td>
<td>60</td>
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<td>185,000</td>
<td>240</td>
</tr>
</tbody>
</table>

* Norepinephrine.  
† Initial count so low that rise insignificant.
prepared from the pure bitartrate powder were given in doses of 0.2 mg. to one patient (Har). Another patient (Bar) received norepinephrine alone.

All samples were collected in glass tubes with heparin as the anticoagulant. Counts were done as promptly as possible. National Bureau of Standards certified hemocytometers and Trenner automatic filling pipets were employed exclusively. The leukocytes in all squares on duplicate counting chambers (totaling at least 600 cells) were counted. Differential counts were made on cover slip preparations stained with Wright's stain. All precautions for accurate counting were observed. Platelet counts were done by the direct method utilizing Toescantin's solution. When the leukocytes number between 5,000 and 10,000 per cu. mm., and all nine squares on each of two chambers filled from a single pipet are counted

**INTRA VENOUS EPINEPHRINE**

**VENOUS BLOOD FROM PULMONARY CONUS**

**ARTERIAL BLOOD FROM FEMORAL ARTERY**

![Graph showing hematologic changes following intravenous administration of 0.2 mg. of epinephrine over 30 and 60 second periods in 4 patients at various leukocyte levels.](image-url)

**TIME IN MINUTES**

Fig. 1.—Hematologic changes following intravenous administration of 0.2 mg. of epinephrine over 30 and 60 second periods in 4 patients at various leukocyte levels. Since the blood samples were obtained from the immediate venous and equivalent arterial side of the lungs, the discrepancies in counts indicate the function of the pulmonary circulation. The rise in leukocytes was more marked in those patients with higher initial counts and with shorter periods of administration. Note the platelet counts in the venous blood are lower than the control values in 3 of the 4 cases.

The 50 per cent confidence limits of the value obtained are ± 4.5 per cent or ± 8.5 per cent at 70 per cent confidence limits. This does not include the added significance of serial results. Differences in platelet numbers of less than 100,000/ cu. mm. were not considered significant.

**RESULTS**

Leukocyte and platelet counts in simultaneously drawn venous and arterial blood were determined, following the intravenous administration of epinephrine in twelve patients with neoplastic diseases (table 1). Within 30 to 120 seconds after the initiation of administration of the epinephrine, in 9 instances the leukocyte counts in the arterial blood increased either to a greater degree or
more rapidly than those in venous blood. In one patient (Wey) with a marked persistent leukopenia, the arterial rise was slight and not considered beyond the limits of error for single counts although the consistency of serial counts lends added significance (fig. 1). The rise in count continued for 60 to 120 seconds following the completion of the injection and persisted for 2 to 3 minutes before it gradually declined. The accompanying rise in the venous blood usually followed the arterial rise by 30 to 60 seconds and occasionally later exceeded the magnitude of the arterial rise. A consistent arteriovenous difference of leukocytes was present whether the blood was obtained from the right heart or from a peripheral vein (fig. 2). In the remaining cases, the leukocyte rise was simultaneous in the arterial and venous blood. These changes occur in leukemic as well as nonleukemic patients (figs. 2, 3A and B). The average leukocyte rise in the 11 patients following the intravenous administration of commercial epinephrine was +20 per cent in the venous blood and +52 per cent in arterial blood.

In 4 patients, the platelet counts increased over 100 per cent in the arterial
blood with greater fluctuation and less consistency than the leukocyte numbers (table 1, figs. 1 and 2). The venous blood samples showed a decrease in platelet numbers of over 50 per cent in 4 instances. In 10 instances there was a discrepancy of greater than 50 per cent between the arterial and venous platelet number. In these studies the arterial blood more frequently contained more platelets than the venous blood.

**Fig. 3A.**—Leukocyte changes following epinephrine in a patient with lymphatic leukemia. Note the initial rise is mainly in the immature lymphocytes in the arterial blood and after two minutes the mature lymphocytes appeared in the venous blood. The rise of leukocytes in the arterial blood preceded the venous rise by 30 to 60 seconds.

**Fig. 3B.**—Car. Male, age 34. Leukocyte and platelet changes following epinephrine. Slow rise after an initial fall in leukocyte level in the arterial blood after epinephrine which reached a high of 660,000 per cu. mm. The changes were due mainly to immature granulocytes. The platelet level in the venous blood shows a marked fall. Many of the venous specimens were discarded because of clot formation within the collecting tubes despite excess heparin and no similar findings on simultaneous samples obtained from the artery.

In one patient with myelogenous leukemia (Bar) 0.1 mg. of norepinephrine caused a venous leukocytosis which exceeded the arterial count. In patient Har, 0.2 mg. of l-epinephrine caused greater leukocytosis than 0.2 mg. of norepinephrine (fig. 4). There was, however, a greater discrepancy between arterial and venous platelet number with norepinephrine than with l-epinephrine. In this patient (Har) following the norepinephrine the venous leukocytosis also preceded that in the arterial blood. Little change in platelet counts occurred.

The leukocytosis appears to be diphasic (figs. 1 and 2). The differential counts
showed the initial arterial rise to be primarily in the granulocytic series (figs. 1 and 2). The later increases in arterial and venous blood were caused principally by the lymphocytes. In general, changes in the arterial blood were more marked with the larger doses of epinephrine, and when the epinephrine was administered over shorter periods of time. No toxic or untoward reactions were observed with

**Fig. 4.—Comparison of leukocyte and platelet changes following l-epinephrine and norepinephrine.**

the administration of the doses of epinephrine used in this investigation. The erythrocyte counts and hematocrit determinations showed no significant changes.

The usual systemic effects of epinephrine and its derivatives were observed in all patients. In general, the increase in leukocyte number occurred prior to or with the rise in systemic blood pressure. In most instances the systemic effects
and blood pressure elevation were completely dissipated within 5 minutes after the injection, at a time when the cellular rise was still evident.

DISCUSSION

Simultaneous intravascular sampling of the venous and arterial sides of the pulmonary circulation in man has permitted a precise and accurate examination of the ingress and egress of formed elements of blood into and from the lungs. The arterial leukocytosis and thrombocytosis consistently appeared immediately after the intravenous administration of epinephrine and in most instances preceded significant alterations in the venous blood. When venous blood was obtained from the right ventricle or pulmonary artery, the increased number of formed elements in the arterial blood can be presumed to come from the lungs. In the remaining studies, where the venous blood was sampled from a peripheral vein the findings also support the conclusion that the lungs were the source of the cells. The constancy of the hematocrit and erythrocyte values excludes hemodilution or hemoconcentration as factors in the blood changes that were recorded.

The immediate and persistent appearance of increased numbers of leukocytes in the arterial blood in the absence of any similar venous blood alterations appears to exclude the spleen and bone marrow as the source of the cells, at least in the early stages of the experiment. The ultimate rises in the venous blood leukocyte counts may be a reflection of the arterial leukocytosis after passage of the blood into the venous circulation but it could also represent a considerable release of leukocytes from any reservoir of cells eventually emptying into the vena cava.

Since the venous blood failed to show any significant platelet increases, it must be presumed that under these circumstances the lungs were the source of the arterial thrombocytosis that was observed. Howell and Donahue found higher platelet numbers in the left heart than in the right heart blood of dogs. They demonstrated megakaryocytes within the lung parenchyma and concluded that the lungs were a source of platelets in the dog. This conclusion has been contested by a number of investigators although the original experiments of Howell and Donahue have not been exactly reduplicated. Fidlar and Waters found platelet increases in the arterial blood only during the initial phases of blood perfusion of the dog heart and lung preparation. However, they employed only one-fourth of the dogs blood volume which was continually perfused. These authors did not mention the possibility that the blood itself may contain other precursors of the platelets which may be formed and/or stored within the lung.

The decrease in platelet number in the venous blood from the control level while the platelets in the arterial blood are maintained at or above the original number suggests that the platelets are being removed at some site between the arterial blood and the right ventricle or pulmonary artery. A decrease in venous platelet number was not observed when the samples were obtained from the basilic vein.

The consistently elevated platelet number in arterial blood with a low venous platelet count indicates that the control of the number of circulating platelets
in arterial blood is independent of the venous platelet number under the conditions of this study.

The lungs are optimally located to deliver large quantities of leukocytes and platelets more rapidly into the circulation than the bone marrow, spleen, liver or other hematopoietic sites. The sizable and ready source of leukocytes and platelets within the pulmonary circulation shown by these studies warrants further investigation of other types of leukocytosis and thrombocytosis with specific attention to the lungs as the possible source of these elements.

**SUMMARY**

1. The leukocyte and platelet contents of arterial and venous blood of 12 patients were determined simultaneously during and following the intravenous administration of 0.1 to 0.3 mg. of epinephrine, l-epinephrine or norepinephrine.

2. Within 30 to 60 seconds after the start of the epinephrine administration, an initial arterial leukocytosis and thrombocytosis occurred in 10 and 8 instances respectively and continued for at least 5 minutes before it declined. A leukocytosis also occurred in the venous blood but followed the arterial rise by 30 to 120 seconds.

3. It is concluded that the initial phase of the leukocytosis and thrombocytosis following intravenous epinephrine infusion is primarily from the pulmonary circulation.

4. The data indicate that the pulmonary circulation in man is a sizable reservoir of leukocytes and platelets which may be readily discharged into the circulation under proper stimulation.

**REFERENCES**


RELEASE OF LEUKOCYTES AND PLATELETS


The Release of Leukocytes and Platelets from the Pulmonary Circulation by Epinephrine