Arteriovenous Shunting in Patients with Multiple Myeloma and High-Output Failure

Sabahat İnanir, Rauf Haznedar, Sevil Atavci and Mustafa Ünlü
Departments of Nuclear Medicine and Hematology, Gazi University Medical Faculty, Beşevler, Ankara, Turkey

High-output cardiac failure is one of the cardiovascular problems associated with multiple myeloma and frequently seen in patients with extensive bone lesions. The purpose of this study was to search arteriovenous shunting in patients with multiple myeloma and cardiac failure. **Methods:** After the exclusion of other causes of congestive heart failure, 11 patients whose cardiac indices were higher than or equal to 4 liter/min/m^2 were selected for the study (7 women, 4 men; mean age 59.64 ± 8.92 yr). All patients had Stage II-III disease and femoral involvement in radiological examination. Arteriovenous shunting was determined by means of intra-arterial injection technique of ^{99m}Tc-macroaggregated albumin (MAA) particles. A quantitative analysis of all scans was performed, and the results were correlated with cardiac index. **Results:** Mean cardiac index was 4.33 ± 0.36 liter/min/m^2 in the study group. In all cases, arteriovenous shunting was detected (18.70% ± 17.29%), and inhomogenous, increased radioactivity accumulation was revealed in the femoral region (lesion-to-background ratio 2.71 ± 2.08). This zone corresponded to the area of infiltration in a radiograph. A significant correlation was found between shunting values and cardiac indices ($r = 0.7899$, $p = 0.004$, Spearman). Although all patients had varying degrees of anemia, we did not find such a relationship between the degree of anemia and cardiac index. **Conclusion:** Arteriovenous shunting within involved skeleton contributes significantly to the development of high-output cardiac failure in multiple myeloma.

Key Words: multiple myeloma; arteriovenous shunting; cardiac failure; radionuclide angiography; technetium-99m-macroaggregated albumin

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Diffuse bone marrow infiltration is a characteristic of multiple myeloma. Arteriovenous shunting within the bone infiltration has been proposed as a contributing factor to high-output congestive heart failure (*1,2*). This hypothesis and the possibility of microscopic shunting in the bone marrow are yet to be fully explained. It is documented that the high-output state was more frequently seen in patients with extensive bone lesions (*2*), and these patients responded well to efficient chemotherapy (*3*).

To determine arteriovenous shunting, the Doppler technique and angiography have been used (*1,2,4*). Using radiolabeled particles (either macroaggregated albumin (MAA) or albumin microspheres), arteriovenous shunting can be demonstrated even at a microcirculatory level (*5–8*). Technetium-99m-MAA, as a particulate perfusion radiotracer, is completely trapped by the first line of microcapillary bed after intra-arterial injection. When there is arteriovenous shunting, bypassing fraction through these short-circuits is accumulated by the pulmonary vasculature. After intra-arterial injection, the detection of radiolabeled particles in the pulmonary vascular bed is an evidence of arteriovenous shunting within the region studied. This technique has been used successfully not only in the diagnosis and quantitation of arteriovenous shunting but also in localizing the site of shunting (*5,9*).

Concerning the pathogenetic mechanism of high-output cardiac failure, we investigated the presence and effect of arteriovenous shunting within the bone lesions of multiple myeloma and its relationship with high-output state.

MATERIALS AND METHODS

Eleven patients were included in this study (7 women, 4 men; age range 45–71 yr; mean age 59.64 ± 8.92 yr) after the exclusion of the other causes of cardiac failure. Written informed consent was provided by all patients. The cardiac index was measured using an indicator dilution method. Only patients whose cardiac indices were high or on the upper limit of normal were selected for the radionuclide study (≥4 liter/min/m^2). All patients had extensive disease, Stage II or III according to SWOG criteria. Femoral involvement was present in all patients.

Thirty-seven MBq ^{99m}Tc-MAA (10–60 μm in diameter, approximately 5×10^4 particles) were injected into the cannula, placed in the femoral artery at the lesion site (2 left, 9 right) and flushed through with saline. After an equilibrium time (2–3 min), a static image was acquired from thoracoabdominal region for 1 min (64 × 64 matrices, 140-keV, 20% energy window, GE XR/T (GE, St. Albans, Herts, England) gamma camera interfaced with Starcam 4000 computer (Starcam, Milwaukee, WI) and LEAP collimator and followed by whole-body imaging. After the arterial phase imaging, the same dose of ^{99m}Tc-MAA was injected intravenously through the antecubital vein, and thoracoabdominal and whole-body images were acquired.

To quantify shunting (Fig. 1), regions of interest (ROIs) were drawn over the midzone of the right lung and left upper abdomen from thoracoabdominal images in the arterial and venous phase images (7 × 7 pixel size). Arteriovenous shunting was calculated using total counts from these reference regions (A_{lung}, A_{body}, V_{lung}, V_{body}, respectively) and the formula below (*5,8*):

$$\% \text{ arteriovenous shunting} = (A_{lung} \times V_{body})/(A_{body} \times V_{lung}).$$

It is considered that V_{lung} counts reflect 100% shunting, but this assumption needs correction for unbound technetium or background activity. For this reason, A_{lung}:V_{lung} ratio should be corrected by V_{body}:A_{body} ratio.

In the statistical analysis, Spearman's rank test was used for correlation. A two-tailed significance was considered ($p < 0.05$).

RESULTS

All 11 patients had 90% plasma cells in the bone marrow and extensive bone lesions (Table 1). The cardiac index was 4.33 ± 0.36 (4–5.10) in the study group. Scintigraphically, arteriovenous shunting was observed in all of the patients (mean shunting value was 18.70 ± 17.29, ranging from 4.80%–47.70%). Shunting ratios were well correlated with cardiac index ($r = 0.7899$, $p = 0.004$; Fig. 2). Although all 11 patients had varying degrees of anemia, hemoglobin and hematocrit

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For correspondence or reprints contact: Sabahat İnanir, MD, Bayindir Medical Centre, Department of Nuclear Medicine, TR-06520, Sogutozu, Ankara, Turkey.

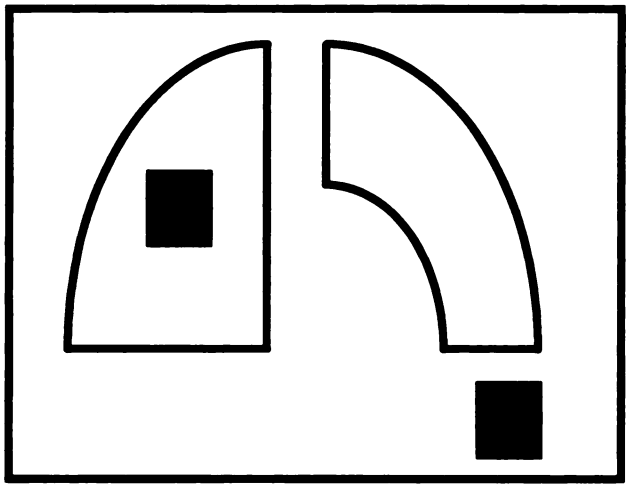

FIGURE 1. ROIs drawn over the midzone of the right lung and the left upper abdomen in the thoracoabdominal images acquired at the arterial (A) and venous phase (V). Venous phase reflects 100% shunting and postintra-arterial counts in the lung reflect bypassing particles. A ratio of arteriovenous shunting can be calculated from these counts by the formula $(A_{lung} \times V_{body})/(A_{body} \times V_{lung})$.

values (9.75 ± 0.54 g/dl and 29.28% ± 1.44%, respectively) did not show any correlation with cardiac indices. In addition, inhomogenous, increased radioactivity accumulation was revealed in the areas corresponding to femoral infiltration of all patients (Fig. 3). The lesion-to-background ratio of femoral lesion was determined as 2.71 ± 2.08 using mean counts per pixel in the femoral and background ROIs (lesion ROI was drawn over the femoral bone between the upper and lower limits of MAA collections, and background ROI was placed to the adjacent, normally perfused soft tissue). However, there was no correlation between arteriovenous shunting values and lesion-to-background ratios in scintigraphic analysis.

DISCUSSION

High output congestive heart failure, hyperviscosity syndromes and amyloid heart disease are cardiovascular manifestations of multiple myeloma (*10*). Anemia and increased plasma volume may cause high-output heart failure in myeloma patients (*10,11*). These patients respond to specific chemotherapy, but the correction of anemia or supportive therapy do not ameliorate failure symptoms (*1–3*). Two explanations have been proposed for high-output failure in myeloma patients. First, arteriovenous shunting and a humoral factor affect cardiac

TABLE 1
Study Results

Patient no.	Age (yr)	Sex	A-V shunting (%)	Cardiac index	Stage	Immunoglobulin type
1	71	F	47	5.1	3B	kappa
2	51	M	39.4	4.5	3B	Ig A, lambda
3	45	F	8.53	4.2	2A	kappa
4	63	F	4.8	4.1	3A	Ig A, kappa
5	56	F	11.2	4	3B	Ig G, kappa
6	63	M	10	4.2	2A	Ig a, lambda
7	68	M	5.3	4.1	3B	lambda
8	68	F	47.7	4.8	3B	kappa
9	46	F	7.5	4.1	2A	kappa
10	62	F	19.2	4.5	2A	Ig G, lambda
11	63	M	5.1	4	2A	Ig G, lambda

A = arterial phase; V = venous phase.

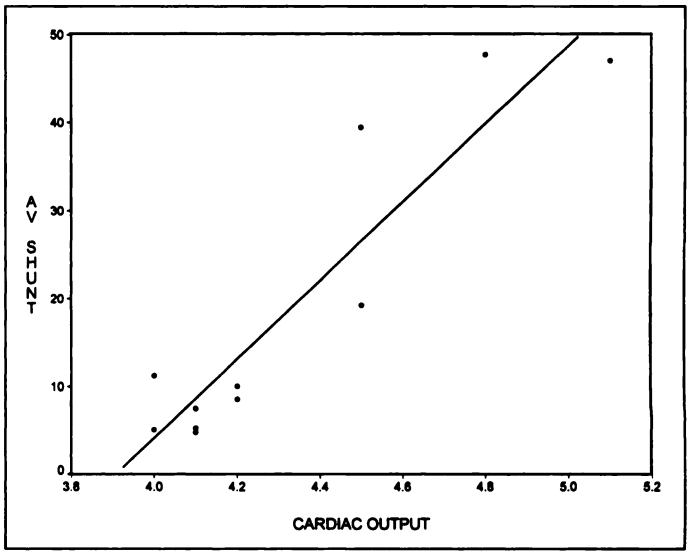

FIGURE 2. Correlation between shunting ratio (%) and cardiac index (liter/min/m^2).

function and peripheric vascular resistance. Tamir et al. (*12*) reported a case with high-output cardiac failure and primary plasma cell leukemia in which chemotherapy resulted in a significant fall in cardiac index. They thought that the soluble factors released from malignant plasma cells may affect peripheric vascular tone and/or inotropi or chronotropi of the heart. It

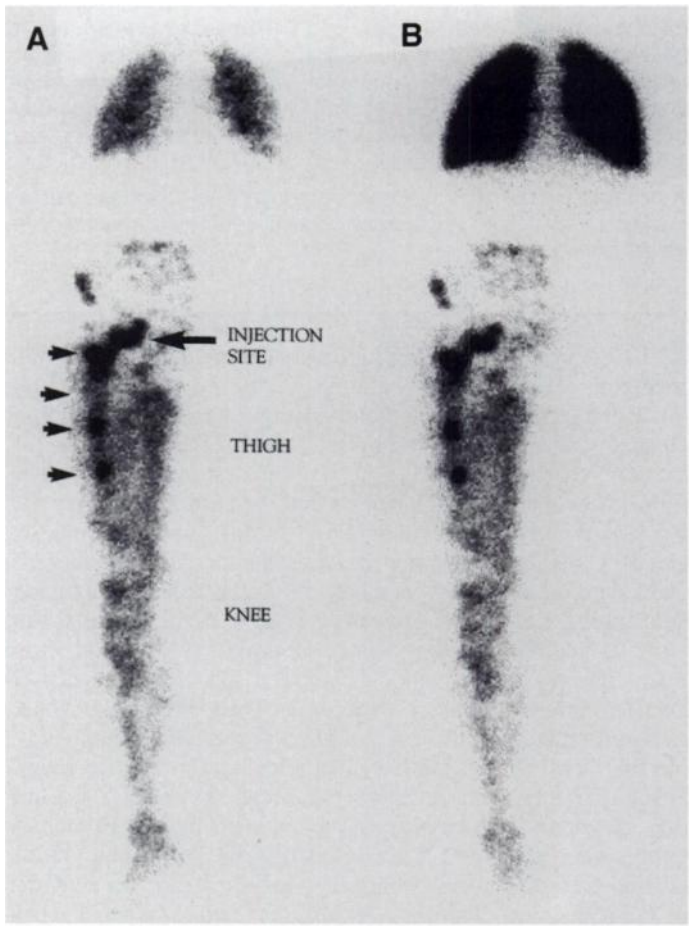

FIGURE 3. A case example with high shunting ratio. Arterial (A) and venous phase (B) images. Cardiac index and shunting ratio were calculated as 5.1 liter/min/m^2 and 47%, respectively. After the intra-arterial injection, concentration of the radiolabeled MAA particles in the lung fields and increased irregular radioactivity accumulation in the femur can be seen (small arrows).

is possible that the decreased tumor volume, as a result of effective chemotherapy, might lead to a reduction in the secretion of vasodilatory substances responsible for shunting. Second, decreased systemic vascular resistance also has been reported in well-defined myeloma patients.

The association of myeloma, arteriovenous shunting and high-output failure was demonstrated by Sanchez et al. (*1*), but they could not determine the exact amount of shunting. In their case, obliteration of abnormal pelvic vessel improved cardiac symptoms and cardiac output. This observation can aid understanding of why these patients are unresponsive to the correction of anemia or supporting therapy with digitalis and diuretics. Embolization of abnormal communication and efficient chemotherapy seem to be more appropriate therapeutic approaches when treating cardiac failure in these patients. Judson et al. (*3*) presented a case in which high-output cardiac failure completely disappeared after successful treatment of multiple myeloma, and they concluded that the high output can be attributed directly to active myeloma requiring efficient chemotherapy.

Our results showed the hypervascular nature of myelomateous lesions and the presence of significant arteriovenous shunting (Fig. 3). The association of increased ^{99m}Tc-MAA trapping in the lesions with accumulation of ^{99m}Tc-MAA particles in the lung fields after intra-arterial injection suggests a marked increase in the number of microcapillary vessels of variable caliber and reflects the presence of an intact capillary bed as well as abnormal communications within the involved bone. The angiographic findings in multiple myeloma include diffuse and inhomogenous contrast uptake in lesions, early venous drainage and rapid arteriovenous shunting (*4*). The advantages of the radionuclide method are that it is able to demonstrate the physiologic effect of arteriographically demonstrable or undemonstrable disease (i.e., it allows the determinations of alterations even at microcirculatory level), to quantify the degree of arteriovenous shunting and to demonstrate the distribution of perfusion to the extremity (*7*). In addition, it has low radiation dose and no side affects. Angiography is unable to differentiate early venous filling from physiologic or anatomic shunting (*7*) and also have the risk of contrast-induced renal failure. The efficiency of different therapeutic modalities can be sensitively monitorized using the scintigraphic shunt procedure.

Different quantification methods have been used in the calculation of arteriovenous shunting (*6–8*). Albumin microspheres can be preferred in shunting studies, which are less fragile than macroaggregates of albumin and in relatively uniform size (*7,13*). On the other hand, ^{99m}Tc-MAA also has been used successfully in the documentation and quantification of arteriovenous shunting in patients with osteogenic sarcomas and hepatic neoplasms (*14–16*). In addition, an agreement between decreasing tumor vascularity, decreasing lung activity and clinical indices of therapeutic response has been reported using ^{99m}Tc-MAA particles (*14,15*). In this study, we preferred to perform arterial injection of ^{99m}Tc-MAA at first to observe clearly a bypassing fraction of radiolabeled particles to pulmonary circulation.

In some shunting studies, ^{99m}Tc-pertechnetate has been used as an agent to be injected intravenously. Distribution of this agent represents background activity and establishes a distribution ratio (*6*). In the microsphere technique, a shunting ratio also has been corrected for unbound technetium in suspended solution (*17*). We selected ^{99m}Tc-MAA for intravenous injection, in which complete trapping of the same amount of particles in the pulmonary vascular bed represents 100% shunting. Although we used the same dose and identical radiopharmaceutical for intravenous and intra-arterial injections, the correction to A_{lung}:V_{lung} ratio also was applied for nonspecific activity such as the possibility of free technetium or a fraction of smaller macroaggregated albumin particles small enough to pass capillaries, and then V_{body}:A_{body} ratio was used as an internal correction factor.

It has been suggested that greater blood flow through the hyperperfused, involved bone alone may cause physiologic shunting and heart disease in Paget's disease, in which abnormal arteriovenous communication has not been demonstrated at autopsy, by angiography or scintigraphy (*18*). It is possible that the venous blood draining hyperperfused myelomateous lesions also may contribute to the hyperdynamic state. In addition to the possible effects of anemia, increased plasma volume, vasodilation, decreased peripheric vascular resistance and physiologic shunting, our results demonstrated that anatomic shunts may play an important role in the development of the high-output state in multiple myeloma. The shunting values detected in this study represent only a part of shunting in patients with extensive disease. But it can be speculated regarding the good correlation between shunting and cardiac index that lesions distributed to other sites of the body might have the same degree of shunting, or the major component of shunting might take place within long bones.

CONCLUSION

The ratio of arteriovenous shunting was closely related to cardiac index, suggesting that an increased shunting within infiltration is related to high-output cardiac failure in patients with multiple myeloma.

REFERENCES

1. Sanchez FW, Chuang VP, Skolkin MD. Transcatheter treatment of myelomatous AV shunting causing high output failure. *Cardiovasc Intervent Radiol* 1986;9:219–221.
2. McBride W, Jackman JD, Gammon RS, Willerson JT. High output cardiac failure in patients with multiple myeloma. *N Engl J Med* 1988;319:1651–1653.
3. Judson IR, Gore ME, Tighe J, Nicolson M, McElwain TJ. Resolution of high output cardiac failure following treatment of multiple myeloma. *N Engl J Med* 1989;321: 1685–1686.
4. Laurin S, Akerman M, Kindblom LG, Gunterberg B. Angiography in myeloma (plasmacytoma): a correlated angiography and histology study. *Skeletal Radiol* 1979;4:8–18.
5. Lee MJ, Dowsett DJ, Ennis JT. Peripheral arteriovenous malformation: diagnosis and localization by intraarterial injection of Tc-99m MAA. *J Nucl Med* 1990;31:1557–1559.
6. Ennis JT, Dowsett DJ. Radionuclide angiography: intra-arterial studies. In: Ennis JT, Dowsett DJ, eds. *Vascular radionuclide imaging: a clinical atlas*. London: Wiley; 1983:122–123.
7. Siegel ME, Wagner HN. Radioactive tracers in peripheral vascular disease. *Semin Nucl Med* 1976;6:217–230.
8. Siegel ME, Stewart CA. Peripheral vascular diseases. In: Harbert J, Da Rocha F, eds. *Textbook of nuclear medicine*. Philadelphia: Lea and Febiger; 1984:467–468.
9. Blisnak J, Staple TW. Radiology of angiodysplasias of the limb. *Radiology* 1974;110: 35–44.
10. Crummy AB, Stegharts MF, Turski PA, et al. Digital subtraction angiography: current status and use of intra-arterial injection. *Radiology* 1982;145:303–307.
11. Waldenstrom J. Diagnosis and treatment of multiple myeloma. New York: Grune and Stratton; 1970:111–116.
12. Tamir R, Lewin RF, Inbal A, Heller I, Theodor E. High output cardiac failure as a presenting symptom of plasma cell leukemia. *Isr J Med Sci* 1985;21:679–682.
13. Bolles TF, Kubiatowicz DO, Evanc RL, Grotenhuis IM, Nora JC. Tc-99m labelled albumin (human) microspheres (15–30 μm): their preparation, properties and uses. *Radiopharmaceuticals and labelled compounds*. Vienna; International Atomic Energy Agency; 1973:151–167.
14. Kim EE, Legaspi JR, Haynie TP, Wallace S. Transcatheter infusion of Tc-99m MAA for predicting response of intra-arterial chemotherapy in osteogenic sarcoma. *Eur J Cancer* 1985;21:35–42.
15. Bledin AG, Kantarjian HM, Kim EE, et al. Tc-99m labelled macroaggregated albumin in intra-hepatic arterial chemotherapy. *Am J Roentgenol* 1982;139:711–715.
16. Roos JC, Teule JJG. Intra-arterial infusion of Tc-99m MAA: a case of highly selective targeting of liver metastases and shunting. *Clin Nucl Med* 1994;19:219–220.
17. Rhodes BA, Rutherford RB, Majana VL, Greyson ND, Wagner HN. Arteriovenous shunt measurements in extremities. *J Nucl Med* 1972;13:357–362.
18. Rhodes BA, Greyson ND, Hamilton JR, et al. Absence of anatomic arteriovenous shunting in Paget's disease. *N Engl J Med* 1972;287:686–689.