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EDITORIAL

Detection of Cardiovascular Infections with Radiolabeled Leukocytes

Cardiovascular infections usually localize to damaged areas of the endothelial wall, areas of thrombosis or prosthetic materials, such as heart valves or grafts. These infections may also spread to form perivascular abscesses. Vascular infections and perivascular abscesses are associated with a high morbidity and mortality if definitive antibiotic and surgical treatment are not instituted immediately. Since clinical symptoms and physical findings are frequently not diagnostic for the presence of infection, nor do they always localize the site, invasive and noninvasive imaging methods are necessary for accurate evaluation. There are two distinct and usually complementary imaging approaches to diagnosis: anatomic and physiologic. The anatomic methods, computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound and contrast arteriography have high spatial resolution that provide exquisite detail of the vascular and perivascular space. If the only step necessary for diagnosis was anatomic definition, physiologic methods would be unnecessary. However, hematomas and seromas next to a vascular graft or native vessel have the same anatomic appearance as an abscess, and noninfected intravascular thrombi, atherosclerotic plaques or prosthetic valves may have the same anatomic appearance as those that are infected. Thus, anatomic methods accurately define cardiovascular structures, but are not specific for diagnosis of cardiovascular infections. In addition, CT and arteriography require intravascular contrast injections for best results, and these cannot be used safely in all patients. Contrast agents are not available for MRI, and cardiac and whole-body ultrasound cannot provide good quality technical studies on all patients, especially those with prosthetic valves. For these reasons, techniques utilizing a physiologic approach are needed for accurate, safe and specific diagnosis of cardiovascular infections.

Radionuclide approaches to identification of cardiovascular infection use radiolabeled, physiologic tracers to detect and localize sites of infection (*1*). Spatial resolution is inferior to anatomic imaging methods due to lower information density, higher background activity and the inherent limitations of radioactive decay. The basic approach involves the identification of a specific target present in high concentrations in the area of infection or that accumulates over time. Traditional targets have included leukocytes, components of the infecting organism or the various protein components present with inflammation. Radiolabeled monoclonal antibodies directed to leukocyte antigens allow in-vivo labeling and have potential for cardiovascular detection of infection. The ideal agent would accumulate rapidly in high concentration at an infected site following intravenous injection and be rapidly cleared from the blood to lower background activity. Detection of vascular or perivascular infections are ideally suited for this approach. There is easy access of the radiolabeled probe to the site of infection and renal, splenic, bone marrow or hepatic clearance, in combination with a large volume of distribution, result in a low background activity in a short time period.

Successful use of radiolabeled leukocytes have been reported for prosthetic valve endocarditis (*2*), detection of large valvular vegetations (*3*) and identification of vascular graft infections (*4,5*). Leukocyte scintigraphy has a useful role only in certain types of endocarditis. That is, only in the presence of increased numbers of leukocytes in association with large vegetations and extensive areas of tissue destruction or abscess formation will there be sufficient uptake to allow imaging. Thus, the sensitivity of this technique will be low in those cases of subacute endocarditis associated with small surface vegetations and minimal tissue destruction. Leukocyte scintigraphy will not be useful for endocarditis screening in patients with underlying cardiac abnormalities who experience episodes of transient bacteremia. Radiolabeled leukocytes are clinically useful in the identifica-

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tion of prosthetic graft infections, especially with abscess formation. Anatomic imaging methods are especially limited due to the creation of imaging artifacts by the prosthetic valves. Since the ^{111}In radiolabeling method used in most studies is very nonspecific, contamination with radiolabeled platelets and red blood cells may give false-positive results caused by enhanced uptake in areas of hemorrhage and thrombosis (*6*). Indium-111-labeled human polyclonal immunoglobulin G has been used in 25 patients with vascular grafts and reported to have a specificity of 100% and a sensitivity of 91% for detection of infection (*7*). These results are very promising and will require further validation.

As reported by Ben-Haim and colleagues in this issue of the *Journal*, ^{111}In-labeled leukocytes also have a role in the diagnosis of mycotic aneurysms. In six patients, CT and MRI identified areas consistent with infection, thrombosis, seroma or hemorrhage, but could not differentiate between these possibilities. Leukocyte imaging provided important information that allowed a diagnosis to be made correctly in six of seven patients. In one patient, sites of infection in the gallbladder and surgical site were also identified, in addition to an infected left common iliac pseudoaneurysm. Thus, surveys for other possible sites of infection can be performed easily by leukocyte scanning.

Although results suggest excellent detection of cardiovascular infections, improvements in this area can still be made. These include radiolabeling with other ^{111}In complexes or ^{99m}Tc, the use of SPECT and improved methods for isolating a pure population of leukocytes.

Despite the high energy, long half-life and low dose of administered activity, ^{111}In is the most frequently used radioisotope due to ease of labeling, high yields of viable cells and the extensive clinical experience acquired over 15 yr (*8,9*). Both oxine and tropolone form a 3:1 complex with ^{111}In. Indium-111-oxine is a highly lipophilic ligand that readily diffuses across leukocyte membranes and dissociates into oxine, which diffuses out of the cells and is removed by washing, and ^{111}In, which is retained in the cytoplasm by binding to intracellular proteins. Unlike the oxine form that requires plasma-free leukocyte preparations, ^{111}In-tropolone allows labeling in small volumes with plasma, and this may improve leukocyte viability and function. However, this agent is not approved for clinical use in the United States.

Leukocytes have also been successfully labeled with ^{99m}Tc-sulfur colloid and ^{99m}Tc-hexamethylpropyleneamine (HMPAO) (*10,11*). The relative merits of ^{99m}Tc versus ^{111}In labeling have been recently reviewed (*12*). The use of ^{99m}Tc allows administration of a higher radiation dose, high count acquisition and wider availability. Since leukocyte migration into vascular and perivascular infections is rapid, the shorter half life is not a problem for detection. Although SPECT imaging is possible with ^{111}In-labeled leukocytes, use of a ^{99m}Tc label will provide better quality images and improved contrast resolution. This should result in improved sensitivity.

Improvements are also possible in isolation and purification of leukocytes. Leukocyte separation is routinely performed using acid citrate dextrose sedimentation, hetastarch and differential centrifugation to obtain platelet-poor, leukocyte-rich plasma. This method is simple to perform and produces a high yield of viable leukocytes that retain chemotaxis and the ability to bind and kill bacteria. However, the ease of leukocyte separation using this method is offset by contamination with platelets and red blood cells. Since the ^{111}In-oxine radiolabeling method is very nonspecific, the final preparation consists of platelets, leukocytes and red blood cells. Thus, in-vivo uptake may be nonspecific for leukocyte accumulation in an area of infection, and areas of thrombus formation may incorporate ^{111}In-labeled platelets and red blood cells.

Other methods of cell separation are available that produce a higher leukocyte purity (*9*). Ficoll-Hypaque differential density centrifugation, elutriation and flow cytometry methods are effective, but the additional time and equipment required have limited their use in most clinical settings.

Thus, radiolabeled leukocytes are complementary to anatomic imaging methods in the identification of cardiovascular infections because: they have a higher specificity in patients, in whom anatomic approaches cannot clearly separate infected from noninfected fluid collections; technically adequate studies can be obtained in most patients; total body surveys can be performed easily; and, since contrast injections are not required, they are safer.

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