

# Noninvasive Assessment of Coronary Arteries in Patients with Hematologic Disorders

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## ABSTRACT

Hematological conditions and their treatments have an increased risk of cardiovascular events, and invasive interventions have a higher risk of periprocedural complications in this group of patients. The aim of this review was to evaluate the risk of invasive interventions in patients with hematologic disorders and to underline the role of noninvasive cardiovascular screening in patients with hematological disorders such as Hodgkin and non-Hodgkin lymphoma, anemia, hemophilia, thrombocytopenia, polycythemia vera, and leukemia. Based on present knowledge in the field, our opinion is that the screening of patients with hematological diseases is very important to reduce the morbidity and mortality due to cardiovascular events. Noninvasive assessments are suitable for this purpose with a significantly lower risk compared to invasive interventions.

**Keywords:** noninvasive, computed tomography, hematological disorders, screening

## INTRODUCTION

Hematological conditions have an increased risk of cardiovascular complications such as atherosclerosis, thromboembolism, myocardial infarction, and, at the same time, several periprocedural complications like bleeding, thrombosis, and infections after invasive angiography.<sup>1</sup> The incidence of cardiovascular complications is increasing due to the higher survivor rate in patients with hematological disorders.<sup>2</sup>

The aim of this review is to study the risk of invasive interventions in patients with hematologic disorders and to underline the role of cardiovascular screening in this group of patients. We are going to study the importance of computed tomography angiography in patients with hematological diseases, after chemotherapy and/or radiotherapy.

Computed tomography angiography (CTA) has a large scale of indications in patients with a high cardiovascular risk. CTA and coronary artery calcium

scoring are also recommended in asymptomatic patients with low or intermediate cardiovascular risk.<sup>3</sup> CTA also provides information on plaque morphology/vulnerability and allows precise risk stratification. This noninvasive investigation has the potential to complement—and in some cases to completely replace—invasive coronary angiography in daily use.<sup>4</sup>

### **CARDIOVASCULAR SCREENING IN HODGKIN AND NON-HODGKIN LYMPHOMA**

Chemo- and radiotherapy used in Hodgkin lymphoma (HL) treatment has an increased risk of heart disease. The most important long-term side effects of mediastinal radiotherapy and cardio-toxic chemotherapeutic agents are cardiovascular complications such as coronary artery disease.<sup>5</sup> Kupeli S *et al.* studied the incidence of cardiovascular events in patients with HL and reported that the most frequent complication of the treatment was ischemic heart disease in 132 (19%) patients, arrhythmia in 110 (16%), congestive heart failure in 85 (12%), and valvular disease in 77 (11%) patients.<sup>6</sup> Ng AK and Lipshultz *et al.* both reported that the mechanism of cardiovascular injury in their group of patients is multifactorial.<sup>7,8</sup> Endothelial injury of the coronary vessels, the production of several inflammatory and profibrotic cytokines have an important role in the appearance and progression of this disease. Daniëls *et al.* described unpredicted premature deaths from myocardial infarction at early ages following Hodgkin lymphoma and underline the necessity of cardiovascular screening of HL survivors.<sup>9</sup> Kupeli *et al.* considered it necessary to discover minimally invasive methods for a precise description of the coronary arteries as well as the cardiotoxic effect of various pharmacological agents.<sup>5</sup> In a case series that included nine patients, Rademaker *et al.* stated that CTA and calcium scoring are useful methods for the assessment of coronary artery disease (CAD) related to irradiation.<sup>10</sup> Compared to catheter angiography, CTA is a noninvasive method with a high negative predictive value. CTA can reveal the effect of radiation and wall thickening of soft tissues in addition to the vascular lumen. Besides the advantage of having lower costs in comparison to traditional invasive angiography, CTA acquires information regarding the vessel wall and enables the identification of pathologic vessels and additional extravascular abnormalities.<sup>10,11</sup> CTA is also able to detect calcium in the vessel lining, with high sensitivity.<sup>10</sup> However, invasive coronary angiography cannot be recommended based only on coronary calcium scoring, due to its low specificity.<sup>12</sup> In patients with HL the generally

recommended screening methods for cardiovascular diseases are coronary computed tomography (CT) and coronary calcium scoring for coronary artery disease, and conventional echocardiography and tissue Doppler imaging for valvular heart disease. Kupeli *et al.* and Lipshultz *et al.* recommend coronary CT and coronary calcium scoring as screening methods for coronary artery disease and conventional echocardiography and tissue Doppler imaging for valvular heart disease in patients after or under chemo- and radiotherapy.<sup>8,11</sup>

Groacher *et al.* created an algorithm for screening patients with non-Hodgkin lymphoma (NHL), who received mediastinal/thoracic radiotherapy.<sup>13</sup> In patients with signs/symptoms of constrictive pericarditis transthoracic echocardiography (TTE) ± CT or magnetic resonance imaging (MRI) is recommended. In case of patients with acute coronary syndrome (ACS) and suspected coronary artery involvement, invasive coronary angiography and/or functional angiogram is the recommended investigation. In case of patients without ACS symptoms, functional imaging such as stress echocardiography, rest/stress myocardial perfusion imaging (MPI), or stress MRI ± coronary computed tomography angiography (CCTA) is recommended. CT coronary Ca score or CCTA, or functional imaging is recommended for asymptomatic patients within five years post radiotherapy. In another study, Kupeli *et al.* stated that a follow-up consisting of screening for valve disorders with tissue Doppler imaging (TDI), evaluation for CAD by CTA, and coronary calcium scoring should be used for survivors of HL, who have received mediastinal radiotherapy or anthracycline.<sup>5</sup> Girinsky *et al.* used CTA to examine 179 asymptomatic HL subjects, and CTA abnormalities were found in 25% of patients treated for HL.<sup>14</sup> Their findings suggest that CCTA is a good method for identifying patients with no symptoms who have a higher risk for acute coronary artery disease and may need future prophylactic or therapeutic procedures. Groacher *et al.* recommend a low threshold for screening with noninvasive imaging methods, for identifying coronary lesions at early stages where an opportune intervention may reduce cardiovascular morbidity and mortality in malignancy survivors.<sup>13</sup>

### **RISK OF INVASIVE INVESTIGATIONS AND TREATMENTS IN PATIENTS WITH ANEMIA**

In a study that included 5,443 ACS patients from the CardioCHUS Registry, Raposeiras Roubín *et al.* found that the advantage of invasive interventions in patients with severe anemia (hemoglobin <10 g/dl) and non-ST-segment el-

evaluation in ACS is not clear.<sup>15</sup> The management of patients with severe anemia was most often conservative (31.2% vs. 21.0%), and there was a significantly higher mortality in patients with severe anemia after an invasive intervention. Patients with anemia undergoing primary percutaneous coronary intervention (PCI) are at a higher risk for an adverse outcome. Rathoda *et al.* examined 2,178 subjects, of which 419 (19%) were anemic and 1,759 (81%) had normal Hb levels.<sup>16</sup> They reported that anemia (hemoglobin level <13 g/dl) is highly predictive for a poor outcome after primary PCI in comparison with patients with normal serum hemoglobin.

### **THE NECESSITY OF SCREENING AND RISK OF INVASIVE INVESTIGATIONS IN PATIENTS WITH HEMOPHILIA**

The incidence of ischemic cardiovascular disease in hemophilia patients is increased due to the longer life expectancy and the longer exposure to cardiovascular risk factors that affect the general population.<sup>17,18</sup> Patients with hemophilia have a decreased risk of acute coronary events in comparison with the normal population due to hypocoagulability and diminished plaque vulnerability. These patients are less prone to develop acute thrombosis in the coronary arteries, however, they might not be protected from atherosclerosis.<sup>19,20</sup> Arterial thrombosis and myocardial infarction (MI) is not exceptional in patients with thrombophilia.<sup>21</sup> Girolami *et al.* studied 42 patients with hemophilia and atherosclerotic disease, majority of these patients (36 cases) presenting with MI.<sup>21</sup> They observed that the majority of cardiac events appeared after or while receiving FVIII, rFVIIa, prothrombin complex (FEIBA), activated concentrates, prothrombin complex (FEIBA), or desmopressin.<sup>22</sup> Schutgens *et al.* and Mannucci *et al.* underline the necessity to correct clotting factor deficiency in patients with hemophilia before performing a PCI or arterial angiography.<sup>23,24</sup> They recommend a target maximum level of 0.8 UL before PCI, and up to 48 hours after PCI, because a higher level can lead to hypercoagulability and the formation of an occlusive thrombus. Lim *et al.* reported a study which included eight hemophiliacs. Clotting factors were not administered in 60% of the procedures, and bleeding complications (e.g., golf ball-sized groin hematoma) appeared in 17% after invasive coronary angiography.<sup>25</sup> Zwiers *et al.* reported the necessity and importance of cardiovascular screening in patients with hemophilia because they are not protected against the development of atherosclerosis.<sup>26</sup> The authors highlight the importance of determin-

ing the calcium score and subclinical atherosclerosis with multi-slice computed tomography (MSCT) in this group of patients to determine the short- and long-term cardiovascular risk.

### **RISK OF ARTERY CATHETERIZATION IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA AND POLYCYTHEMIA VERA**

The risk of excessive bleeding and thrombosis is increased in patients with extreme thrombocytosis, either of which can complicate cardiovascular surgical and interventional procedures.<sup>27</sup> There are no definitive recommendations in the literature regarding platelet-count control before catheter-assisted cardiovascular intervention.<sup>28</sup> Virchow's triad contains the three major factors that contribute to thrombosis. The first factor is represented by hypercoagulability, which is very common in myeloproliferative diseases such as leukemia, lymphoma, essential thrombocythemia, and polycythemia vera.<sup>29</sup> The second factor is represented by the mechanical injury of the arterial wall, which can occur in artery catheterization or due to circulating leukocytes and platelets in blood stream.<sup>29-31</sup> In 2008, Ruggeri *et al.* presented the results of a large study that found an increased risk of excessive bleeding (7.3%) and vascular occlusion (7.7%) in patients with multiple personality disorder and thrombocytosis.<sup>32</sup> Vidwan *et al.* reported the results of a retrospective study on 3,466 patients undergoing coronary angiography, in which they found significant correlations between the risk of bleeding, vascular complications, and elevated platelet counts. In contrast, thrombocytopenia was not associated with any cardiovascular risk.<sup>33</sup> Ulrich *et al.* presented a case of a patient with essential thrombocytosis who developed digital gangrene after radial artery catheterization. They affirm that patients with marked thrombocytosis and myeloproliferative diseases are at a higher risk for complications of invasive arterial monitoring.<sup>34</sup>

### **CARDIOVASCULAR RISK OF ANTI-LEUKEMIC TREATMENT**

Increased leukocyte count represents a risk factor for cardiovascular events and a negative prognostic factor for coronary artery disease.<sup>35</sup> Naruko *et al.* found in their study that neutrophil infiltration holds an important role in the destabilization of the atherosclerotic plaque.<sup>36</sup> Cancer therapies such as tyrosine kinase inhibitors in patients

with chronic myeloid leukemia represent an increased risk for cardiovascular events (10%).<sup>37</sup> Moslehi *et al.* stated that noninvasive cardiovascular screening is necessary before the start of dasatinib therapy and for patients with cardiopulmonary symptoms receiving treatment.<sup>38</sup> In case of treatment with nilotinib, a close noninvasive cardiovascular monitoring is recommended by the European Medicines Agency, because it can aggravate preexisting atherosclerotic lesions.<sup>39</sup> Another tyrosine kinase inhibitor, ponatinib is linked to an increased risk of thromboembolic events.<sup>40</sup>

## CONCLUSION

In conclusion, cardiovascular screening has an important role in patients with hematological diseases. Chemotherapy and radiotherapy in Hodgkin and non-Hodgkin lymphoma can lead to severe cardiovascular complications. Current studies underline the importance of noninvasive assessments such as computed tomography angiography and calcium scoring to reduce the morbidity and mortality due to cardiovascular events in this group of patients. Hemophilia and myeloproliferative disease also have higher cardiovascular risks. At the same time, they have an amplified risk of periprocedural complications such as hemorrhage, thrombosis, arterial occlusion after/during invasive angiography or angioplasty. Patients with anemia also have a higher mortality after invasive procedures in comparison with patients with normal hemoglobin. In case of leukemia, the highest cardiovascular risk is represented by the anti-leukemic drugs and the infiltration of coronary arteries and atherosclerotic plaques with leukemic cells. The literature stresses the necessity of noninvasive cardiovascular screening in patients with leukemia because of the negative effect of chemotherapy and leukemic cells on the circulatory system.

A small number of articles deal with the role of noninvasive assessments in patients with hematological disorders. Our opinion is that the screening of patients with hematological disease is very important to reduce morbidity and mortality due to cardiovascular events. Noninvasive assessments are suitable for this purpose with a significantly lower risk compared to invasive interventions. Additional data is needed to accurately define the benefits of long-term cardiovascular monitoring in patients with hematologic diseases.

## CONFLICT OF INTEREST

Nothing to declare.

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