CORRESPONDENCE

Myocarditis: Early Biopsy Allows for Tailored Regenerative Treatment

by Dr. rer. nat. Uwe Kühl, Prof. Dr. med. Heinz-Peter Schultheiss
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No Standard Biopsy

There have repeatedly been reports of “almost healthy patients” who underwent endomyocardial biopsy—out of whatever considerations—and then died from cardiac tamponade with complications. The risk of a fatal event is 0.1% (1) to 0.03% (2), that of fatal cardiac tamponade is 0.42%. Certain disorders do not usually constitute an indication for myocardial biopsy—for example, atrial fibrillation without any indication of inflammatory cardiac disease, or moderate arrhythmias (extra systole in patient with unrestricted cardiac function), or re-entry tachycardia caused by an additional pathway, which is never of inflammatory origin. In case of suspected myocarditis with unrestricted cardiac functioning, myocardial biopsy is indicated as a measure of last resort only. The article remains too euphoric in its key messages because ultimately, only very few inflammations can be treated causally (for example, giant cell myocarditis); many forms of myocarditis heal spontaneously. Patients with uncharacteristic symptoms and moderate disorders should not undergo biopsy by default, since this exposes them to unnecessary risks and causes unnecessary expense. I would have wished for a more critical assessment of the method in a review article that is accessible to a wide range of doctors.

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REFERENCES

1. Murphey JG, et al.: Endomyocardial biopsy in myocarditis Chapter 15. <http://myocarditisfoundation.org/pdfs/From-Bench-to-Bedside-chapter-15.pdf>
2. www.uptodate.com/contents/endomyocardial-biopsy?source=search_result&search=endomyocardial+biopsy&selectedTitle=1%7E96
3. Kühl U, Schultheiss HP: Myocarditis—elderly biopsy allows for tailored regenerative treatment. *Dtsch Arztebl Int* 2012; 109(20): 361–8.

Dr. med. Mathias Brinschwitz
Facharzt für Innere Medizin, Marburg
privat@praxis-dr-brinschwitz.de

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The author declares that no conflict of interest exists.

Therapeutic Recommendations Were Non-Specific

The problem of differential diagnosis and treatment of myocarditis is one of the biggest challenges in internal medicine, and it is for this reason that the value of myocardial biopsy is often underestimated. While fully supporting the authors on this point, I wish to add some comments from a clinical-immunological perspective.

In order to secure an unequivocally confirmed diagnosis, any case of suspected myocarditis that is not primarily due to infectious or toxic processes should be diagnostically evaluated specifically for immunological-rheumatic etiology.

If the patient has a systemic-immunological disorder rather than myocarditis only, the respective therapeutic regimen should immediately change according to the recommendations for the underlying disorder as the systemic aspect then becomes the therapeutic priority. Furthermore, it is to be expected that, after the suggested (minimum) duration of therapy of 6 months in patients with autoimmune myocarditis, a (possibly avoidable) episode of the underlying disorder may occur. Fortunately, in this situation, a much wider therapeutic repertoire is available for these oligosymptomatic, but fundamentally systemic, immunological disorders.

In addition, the therapeutic recommendations listed in the table could have been outlined more specific for routine clinical practice; consistently with the TIMIC study, mention should not be made of “cortisone” or “methylprednisolone,” but a defined dose of prednisolone equivalent (for which gastroprotection with proton pump inhibitors is not automatically necessary, and calcium is now regarded obsolete). A maintenance dose of >5 mg prednisolone equivalent usually also indicates insufficient effect of the immunosuppressive drug. It is furthermore worth mentioning that some of the risk factors not listed in the table should also be considered—for example, mesalazine as a trigger of myocarditis, but also routine vaccinations for chickenpox and diphtheria/tetanus.

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REFERENCES

1. Peter HH, Pichler W, Müller-Ladner U (eds.): *Klinische Immunologie*. München: Elsevier Verlag 2012.
2. Kindermann I, Barth C, Mahfoud F, et al.: Update on myocarditis. *J Am Coll Cardiol* 2012; 59: 779–92.
3. Sagar S, Liu PP, Cooper LT Jr: Myocarditis. *Lancet* 2012; 379: 738–47.
4. Kühl U, Schultheiss HP: Myocarditis—elderly biopsy allows for tailored regenerative treatment. *Dtsch Arztebl Int* 2012; 109(20): 361–8.

Prof. Dr. med. Ulf Müller-Ladner

Justus-Liebig-Universität Gießen, u.mueller-ladner@kerckhoff-klinik.de

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In Reply:

The indication for myocardial biopsy is set out in the recommendations of the European and American medical specialty societies, published by Cooper et al in 2007. According to these, isolated arrhythmias and atrial fibrillation (class III, evidence level III) do not, or only rarely, constitute an indication for myocardial biopsy (reference 4 in our article).

“Almost healthy patients” undergo myocardial biopsy only in exceptions and for good reasons. This is done in full awareness of the facts that these disorders often progress without characteristic clinical symptoms and myocardial function remains intact, and it is impossible to decide clinically whether a viral-infectious component has already resolved or persists at a low level and will cause cardiac damage in the long term. Because often in the early stages, pump function impairment may occur that lasts only a few days and is rapidly reversible (30%) and a proportion of these patients then develop cardiomyopathy after a “problem free interval,” unrestricted cardiac function should not constitute a reason for not undertaking a targeted diagnostic evaluation with a view to gauging potential treatment options.

For myocarditis, mortality rates of 25–56% have been described. Without a biopsy, targeted, causal treatment is impossible. The poorer disease course of untreated patients in the TIMIC study and the more than 50% 5-year mortality associated with untreated enteroadenoviral cardiomyopathies after 10 years (1) prove the necessity for early myocardial biopsy at a time when the myocardium has developed only minimal damage. It goes without saying that the indication for this has to be made for a good reason.

In large centers with experienced examiners, the complication rates associated with myocardial biopsy are lower than in other diagnostic or interventional catheter examinations. Deaths are rare; we have not seen any in the more than 8000 patients examined in our hospital (>50 000 biopsies) (2). Other large centers have reported similar rates. Data from smaller or older investigations series cannot be used as a gold standard, owing to the advanced catheter techniques available today (2).

It is certainly correct that other causes, such as myocardial involvement in systemic and immunological-rheumatic disorders, need to be considered in the diagnosis of myocarditis (when defining an indication for myocardial biopsy) and in the treatment, because these would change the treatment regimen accordingly, as the author correctly stated. If the history or clinical presentation provides relevant pointers, the diagnostic evaluation should be done before defining an indication for myocardial biopsy and should include colleagues from other medical specialties. Other cardiopulmonary disorders are excluded before the suspected diagnosis of myocarditis. The argument regarding cortisone equivalence dosages is justified, although in many therapeutic studies, different dosages of prednisolone or methylprednisolone were given without any difference to the result. In the TIMIC study, patients were initially treated with 1 mg prednisolone. Mesalazine can trigger myocarditis, as can a multitude of other medications not mentioned for reasons of space. We mentioned vaccinations in

Table 1.

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REFERENCES

1. Kühl U, et al.: Interferon-Beta improves survival in enterovirus-associated cardiomyopathy. *J Am Coll Cardiol* 2012; 60: 1295–6.
2. Holzmann M, et al.: Complication rate of right ventricular endomyocardial biopsy via the femoral approach a retrospective and prospective study analyzing 3048 diagnostic procedures over an 11-Year Period. *Circulation* 2008; 118: 1722–8.
3. Deckers JW, Hare JM, Baughman KL: Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol* 1992; 19: 43–7.
4. Kühl U, Schultheiss HP: Myocarditis—elderly biopsy allows for tailored regenerative treatment. *Dtsch Arztebl Int* 2012; 109(20): 361–8.

Dr. rer. nat. Uwe Kühl

Prof. Dr. med. Heinz-Peter Schultheiss

Medizinische Klinik II, Kardiologie und Pneumologie,
Charité – Universitätsmedizin Berlin,
Campus Benjamin Franklin
uwe.kuehl@charite.de

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