Arrhythmogenic cardiomyopathy: what blood can reveal?

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Blood, serum and plasma represent accessible sources of data about physiological and pathologic status. In arrhythmogenic cardiomyopathy (ACM), circulating nucleated cells are routinely used for detection of germinal genetic mutations. In addition, different biomarkers have been proposed for diagnostic purposes and for monitoring disease progression, including inflammatory cytokines, markers of myocardial dysfunction and damage, and microRNAs. This review summarizes the current information that can be retrieved from the blood of ACM patients and considers the future prospects. Improvements in current knowledge of circulating factors may provide noninvasive means to simplify and improve the diagnosis, prognosis prediction, and management of ACM patients.

KEYWORDS Arrhythmogenic right ventricular cardiomyopathy; Biomarkers; Blood; Genetics; Heart failure; Inflammation; microRNA; Plasma; Serum

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Introduction

Blood is an easily accessible tissue, widely exploited in medicine to obtain clinical information at different levels. It serves as a window to monitor health or disease states because of its complex and "flexible" composition. Indeed, the whole set of molecules present in the blood originates from all body tissues, thus reflecting their fitness. In particular, several blood-based tests are routinely used to diagnose a wide number of pathologies, to understand their possible causes, to monitor the state of progression/remission and outcomes after treatment, and to help the choice of appropriate specific therapies as tools for theranostics.

Thus, research is continuously making remarkable efforts to improve the quantity and quality of information retrieved from this tissue. Blood complexity can be unraveled using different approaches, either omics- or hypothesis-driven, the latter usually originating from known molecular mechanisms involved in a specific disease.

Biomarkers are defined as disease indicators that can be measured accurately and reproducibly.¹ In particular, circulating biomarkers have the unquestionable advantage of being noninvasive and usually inexpensive. Despite these advantages, the number of clinical-grade biomarkers is limited, and the validation path of biomarkers possessing high sensitivity and/or specificity for a defined disease is challenging. This issue may be overcome by using a combination of different molecules.

In this review, we applied a structured literature search (Supplementary Methods and Supplemental Figure S1) to summarize the most up-to-date information retrievable from blood samples with regard to arrhythmogenic cardiomyopathy (ACM) patients (Figure 1). Because of their genetic basis, germinal mutations are routinely assessed in blood cells. However, much more information can be potentially unraveled. ACM inflammatory components can be studied through circulating lymphocytes–monocytes and cytokines, as well as possible systemic concomitant infective agents. Cardiac damage can be monitored by detecting released factors as well as circulating microRNAs (miRNAs). Sex prevalence is reflected in blood hormonal modulation. To date, no validated circulating biomarkers are available for ACM, and the few new candidates that have been proposed mainly provide indications about disease progression rather than onset. We speculate that advances beyond the
current knowledge will translate into future extensive exploitation of noninvasive blood tests in ACM.

**ACM**

ACM is a genetic and relatively rare cardiac disease characterized by ventricular fibrofatty substitution and arrhythmias. In the majority of cases, involvement of the right ventricle (RV) is predominant, with a lesser representation of left dominant and biventricular forms.

It mostly affects young men, particularly athletes, as intense physical exercise worsens the disease phenotype. Sustained myocardium workload provokes a training-induced heart remodeling that, despite being generally considered as physiological, can induce adverse alterations in predisposed subjects.

ACM onset usually occurs during adolescence and early adulthood. In many cases, nonspecific symptoms, such as syncope and palpitations, arise before the manifestation of overt myocardial dysfunction. Even in the context of well-preserved morphology, histology, and ventricular function, ACM patients may die of sudden cardiac death. As the disease progresses, the myocardial damage becomes evident, and structural anomalies such as regional wall-motion abnormalities, increased myocardial trabeculation, ventricular dilation, and dysfunction appear. At the histologic level, cardiomyocyte death, inflammation, and fibro-adipose substitution are observed.

Currently there is no single gold standard diagnostic test for ACM. The diagnosis is based on a scoring system of “major” and “minor” criteria that include structural and electrocardiographic alterations, tissue characterization, previous arrhythmic events, and family history. In selected cases, a genetic test is recommended.

**Genetics**

Genetic tests are increasingly performed in the diagnostic process for inherited cardiovascular diseases. The opportunity to confirm diagnostic suspects or to identify at-risk relatives using blood samples is widely used in ACM, allowing etiologically based differential diagnosis if clinical presentation is not specific. Since 2000, molecular genetic analysis led to the discovery of many genes associated with ACM. To date, it is known that ACM has mostly a familial occurrence with an autosomal dominant inheritance. Recessive forms are also present, namely, Naxos and Carvajal syndromes, and are associated with a cutaneous phenotype.

The most frequently mutated genes encode for desmosomal proteins, but mutations in nondesmosomal genes are also known. Desmosomes are intercellular junctions that provide cell-to-cell adhesion and influence intracellular transduction signals, through the Wnt pathway, which is impaired in ACM patients. These mutations lead to electrical and mechanical dysfunction of the myocardium. For a list of genes associated with ACM, see Supplemental Table S1.

Genetic testing is initially recommended in 1 proband per family. For each screened individual, cardiomyopathy gene panels could be used when clinical features overlap with other cardiac diseases or, when the phenotype is indisputable, a selected ACM-specific panel could be used. When a causative mutation is identified, predictive genetic testing is applied to ascertain the presence of the disease in apparently
healthy relatives, in order to adopt preventive/follow-up strategies in individuals at risk.

Unfortunately, the genetic cause remains unknown in approximately 50% of probands with routine screening. The success rate of genotyping could depend on several variables, such as cohort ethnicity, proband selection criteria, and the standards applied to understand the pathogenicity of the detected variants. Negative results could be due to the use of techniques that do not allow the detection of copy number variations. Moreover, phenotype misclassification could represent a considerable limit of this analysis. Furthermore, the presence of mutations in genes not yet associated with ACM could be an additional reason for low efficiency.

Notably, compound or digenic heterozygosity is present in up to 18% of ACM patients, indicating that more than 1 pathogenic allele may be involved. Even if the value of genetics in risk stratification is poorly understood, multiple mutations and, possibly, mutations in the PKP2 gene are predictors of more severe prognoses.

Because of this variability, even after genetic tests, ACM diagnosis and risk stratification are still challenging. Recently, different variants previously linked to ACM have been reclassified as variants of uncertain pathogenicity because they have been found also in large screenings of healthy subjects (see the ARVD/C Genetic Variants Database at http://www.arrcdatabase.info for indications on variant pathogenicity). The possible false-positive rate seems to be particularly high. However, when a causal mutation is not detected, the complete exclusion of the disease is not possible.

Genetic and phenotypic overlap between ACM and other types of cardiomyopathy have been reported, particularly with dilated cardiomyopathy, Brugada syndrome, and hypertrophic cardiomyopathy (Supplemental Table S1). In these cases, differential diagnosis is challenging even with the help of blood genetic tests.

The amount of implicated variables clearly defines how complex it is to obtain useful information on ACM genetics. Therefore, a great effort in the interpretation of the results is necessary to define their clinical significance, in addition to constant technical progresses. The advent of low-cost next-generation sequencing, the development of sophisticated analytics tools and models to test the pathogenicity of ACM mutations, and the increased knowledge about disease-associated genes represent significant steps forward in providing genetic diagnosis to patients.

Infections, inflammation, and immunity

An inflammatory milieu with patchy infiltrates in the RV has been observed in ACM hearts. Thus, an inflammation theory was formulated to explain ACM etiology. In particular, it has been proposed that genetic mutations could induce immune alterations contributing to heart-specific inflammatory conditions. The inflammatory process could provoke myocardial injury, followed by a genetically determined aberrant fibro-adipose repair. However, whether inflammation is a primary mechanism or a consequence of mutation-dependent cardiomyocyte death is still unknown. Indeed, inflammation related to necrosis and apoptosis has been reported, involving a feed-forward loop.

Most of the studies investigating ACM cardiac inflammation are based on invasive endomyocardial biopsy analysis to evaluate the presence of macrophages, neutrophils, and mast cells in the RV of ACM patients. Also, the presence of cardiotropic viruses has been reported in the ACM myocardium, possibly contributing to the inflammatory environment. In fact, a correlation between genetic predisposition and viral susceptibility has been proposed. Because the use of cardiac biopsy is limited by its invasiveness, noninvasive techniques based on blood analysis to monitor cardiac inflammation are desirable. The detection of viruses and bacteria in the blood of ACM patients could reflect a cardiac infection. Chronic infections with Bartonella henselae, a bacterial agent associated with endocarditis detected in serum samples, have been proposed to be linked to ACM as a possible cause of nonfamilial ACM cases.

To date, circulating inflammatory mediators in ACM patients have been tested measuring different parameters. The plasmatic levels of the inflammatory marker C-reactive protein (CRP) are higher in the blood of patients with ACM than in those with idiopathic ventricular tachycardia (IVT), often in differential diagnosis. The association of an inflammatory status with the occurrence of arrhythmic events has been postulated because CRP levels significantly increase just after ventricular arrhythmia (VA) occurrence in ACM patients. However, because the CRP values of nonarrhythmic ACM patient subgroups have not been shown as well as those of the IVT cohort immediately after VA, CRP increase might be associated with VA and not with ACM. In addition, higher levels of circulating proinflammatory cytokines have been found in ACM patients compared to healthy controls. Although the inflammatory status of the heart has been associated with disease severity, no studies have correlated circulating cytokine levels to myocardial damage degree.

Myocarditis is often in the differential diagnosis with ACM. However, it has been postulated that myocarditis is a superimposed phenomenon during the natural history of ACM, being associated with an active progression phase. To date, no study has addressed the role of circulating factors in the differential diagnosis between these 2 diseases.

Recently, an autoimmune etiology has been proposed; however, the presence of autoantibodies against desmosomal components in ACM plasma needs to be confirmed in larger cohorts. Thus, to date, a complete characterization of circulating inflammatory/immune response in ACM is still lacking. A large analysis of inflammatory cell mediators, antibodies, and cytokines may help define an ACM-specific inflammatory cascade and improve diagnostic and prognostic processes along with pathogenic mechanisms.

Circulating biomarkers of damage

Heart failure (HF) in ACM is a severe consequence of an advanced cardiac remodeling process. Thus, the exploitation
of different HF biomarkers are proposed for the characterization of ACM late phases. Circulating brain natriuretic peptide (BNP) is routinely used to evaluate the presence and progression of HF and has been shown to be a useful indicator of RV dysfunction in ACM patients due to the reported negative correlation with RV ejection fraction. Of note, BNP is higher in the plasma of ACM vs IVT patients, which aids differential diagnosis. Accordingly, immunohistochemistry performed on endomyocardial biopsies showed no detectable BNP in the RV of IVT patients, whereas positive results were obtained in ACM patients. Similar experiments using the N-terminal fragment of BNP, NT-proBNP, showed its association with RV dysfunction and volumes in ACM. This observation has been confirmed in other studies. The major limitation of the use of BNP and NT-proBNP in association with ACM is its low specificity due to the well-known association with a large number of HF-related cardiac conditions.

In 2009, the chaperone heat shock protein 70 (HSP70) was found to be differentially expressed in failing hearts of ACM patients in comparison to nonfailing hearts, with similar results at the systemic level. Based on in vitro results, circulating HSP70 was proposed to originate from damaged myocardial cells. Other evidences associated HSP70 with inflammation and apoptosis. Similarly to BNP, HSP70 usage is limited by its lack of ACM specificity because it is elevated in patients with dilated cardiomyopathy and ischemic cardiomyopathy.

Likewise, cardiac troponin I (cTnI), a structural protein released into circulation after cardiomyocyte death and a well-established marker of cardiac muscle injury, has been proposed to be associated with ACM. The first evidence was observed in ACM boxer dogs, in which a correlation between cTnI levels and premature ventricular contractions was demonstrated. This was confirmed in humans, highlighting a correlation of cTnI with major arrhythmic events. However, its use in ACM is questionable because troponin increase also has been observed in athletes with ischemia or myocarditis and in agonist athletes after strenuous physical activity.

In 2012, Hong et al proposed bridging integrator 1 (BIN1) as a marker of cardiac functional status and for predicting the risk of development of ventricular arrhythmias in ACM patients with HF. Decreased levels of BIN1 (a regulator of calcium transients and contractility) were found in the blood of ACM patients with HF, suggesting its possible use as biomarker. However, this hypothesis is limited by the observation that BIN1 levels in ACM patients without HF are comparable to those found in healthy controls, thus limiting its usefulness to advanced stages of the disease.

In 2017, Broch et al analyzed the plasmatic levels of interleukin-33 receptor ST2, which was previously associated with cardiac remodeling and fibrosis. They observed a correlation between circulating ST2, right and left ventricular function, and arrhythmia occurrence in ACM. They proposed ST2 as a possible biomarker of disease severity upon validation in prospective studies.

Another described marker of fibrotic substitution in ACM patients, galectin-3 (GAL-3), was found increased in ACM plasmatic samples compared to controls. Strikingly, GAL-3 differential levels between patients with and those without arrhythmic events during the follow-up period were assessed, indicating a GAL-3 predictive value for VA in these patients.

Because ST2 and GAL-3, beside fibrosis, were also associated with inflammation, future investigations should evaluate the correlation with the extent of fibrosis in ACM patients.

Thus, the introduction of the described biomarkers in the clinical scenario for diagnostic, prognostic, or severity evaluation purposes still needs refinements. Many of these circulating biomarkers are used for other cardiac diseases in which HF is a common underlying hallmark. As mentioned, however, ACM patients only show HF signs in the later stage of the disease, so the impact of HF-related biomarker is limited. Similarly, the arrhythmic phenotype of ACM has been associated with other circulating biomarkers, but the lack of specificity for ACM does not allow the use of a single biomarker for diagnosis and patient management.

Sex hormones

Because males are more frequently affected by ACM than females, sex hormones and their correlation to disease severity have been tested. A general increase of testosterone serum levels was found in male and female ACM patients with major adverse cardiac events compared to those without. This is in line with previous results that showed the role of testosterone in the stimulation of arrhythmias. Accordingly, in female patients with arrhythmic events, estradiol levels were lower, indicating a possible cardioprotective role of this sex hormone.

A direct role for sex hormones in ACM cellular pathogenic changes has been proposed using induced pluripotent stem cell-derived cardiomyocytes. In this model, testosterone administration increased apoptosis and lipogenesis whereas estradiol ameliorated these phenotypes, possibly through already described mechanisms. However, hormones are not stable, and several factors could affect their levels. Thus, the clinical use of sex hormone dosage/therapy in correlation with ACM severity remains challenging.

miRNAs

miRNAs are short (22–24 nucleotides) noncoding RNAs involved in several biological and pathologic processes. As a consequence of their regulatory role, expression levels of miRNAs are prone to frequent variations in response to several stimuli, including pathologies such as cancer, cardiovascular diseases, inflammation, and neurological disorders.

In the last few years, miRNAs have attracted the attention of researchers and clinicians because of their potential utility as biomarkers in relation to their presence in almost all biological fluids, including plasma and serum. Notably, with regard to cardiac diseases, several reports have described the diagnostic potential of circulating miRNAs. Few studies have evaluated circulating miRNAs in ACM. We were the first, in 2017, to find a correlation between ACM
and low plasma levels of miR-320a.62 These levels were unaffected by physical activity, a recognized ACM-precipitating factor, suggesting that its modulation in ACM is independent of training-induced heart remodeling. Furthermore, miR-320a was valuable in distinguishing ACM subjects from IVT patients. Interestingly, miR-320a seemed to have mechanistic implications in ACM pathogenesis. It was increased during adipogenic differentiation of human mesenchymal bone marrow cells63 and in regulating the Wnt pathway in human colon cancer cells.64 Thus, it can be expected that deregulated miR-320a expression is related to cardiac cell apoptosis and adipogenesis. The diagnostic value of miR-320a needs to be validated in larger cohorts of ACM patients.

### Table 1

<table>
<thead>
<tr>
<th>Circulating factors</th>
<th>Regulation in ACM</th>
<th>In clinical use</th>
<th>Possible clinical application in ACM</th>
<th>Proposed pathophysiology</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Genetics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DNA from blood cells</td>
<td>Yes</td>
<td>Yes</td>
<td>Diagnosis, Differential diagnosis</td>
<td>Causative genes</td>
<td>Table S1</td>
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<td>Inflammation</td>
<td></td>
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<tr>
<td>Viruses and bacteria</td>
<td>↑</td>
<td>Yes</td>
<td>Severity (HF and arrhythmias)</td>
<td>Cardiac infection enhancing cardiac remodeling</td>
<td>30</td>
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<tr>
<td>Inflammatory cytokines</td>
<td>↑</td>
<td>Yes</td>
<td>Severity</td>
<td>Cause and/or consequence of cardiac injury</td>
<td>32, 33</td>
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<tr>
<td>C-reactive protein</td>
<td>↑</td>
<td>Yes</td>
<td>Differential diagnosis with IVT or myocarditis</td>
<td>Consequence of cardiac injury</td>
<td>31</td>
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<tr>
<td>Biomarkers of damage</td>
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<tr>
<td>Brain natriuretic peptide (BNP)</td>
<td>↑</td>
<td>Yes</td>
<td>Severity (HF)</td>
<td>Consequence of cardiac injury</td>
<td>37, 39</td>
</tr>
<tr>
<td>Heat shock protein 70 (HSP70)</td>
<td>↑</td>
<td>No</td>
<td>Severity (HF)</td>
<td>Consequence of cardiac injury Associated to inflammation and apoptosis</td>
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<tr>
<td>Cardiac troponin I (cTnI)</td>
<td>↑</td>
<td>Yes</td>
<td>Severity (HF), Prognosis (arrhythmias)</td>
<td>Consequence of cardiac injury and cardiomyocyte death</td>
<td>39</td>
</tr>
<tr>
<td>Bridging integrator 1 (BIN1)</td>
<td>↑</td>
<td>No</td>
<td>Prognosis (arrhythmias)</td>
<td>Consequence of cardiac injury</td>
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<tr>
<td>ST2</td>
<td>↑</td>
<td>Yes</td>
<td>Severity (HF and arrhythmias)</td>
<td>Associated to inflammation and cardiac fibrotic remodeling</td>
<td>49</td>
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<tr>
<td>Galectin-3</td>
<td>↑</td>
<td>Yes</td>
<td>Prognosis (arrhythmias), Severity (HF)</td>
<td>Associated to inflammation and cardiac fibrotic remodeling</td>
<td>51</td>
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<td>Hormones</td>
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<tr>
<td>Sex hormones</td>
<td>↓↑</td>
<td>Yes</td>
<td>Prognosis (arrhythmias), Severity (HF)</td>
<td>Direct effect on cardiomyocyte lipogenesis and apoptosis</td>
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<td>MicroRNAs</td>
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<tr>
<td>miR-320a</td>
<td>↓</td>
<td>No</td>
<td>Differential diagnosis with IVT</td>
<td>Targets Wnt pathway, regulates apoptosis and adipogenesis</td>
<td>62</td>
</tr>
<tr>
<td>miR-144-3p, 145-5p, 185-5p, and 494</td>
<td>↑</td>
<td>No</td>
<td>Differential diagnosis with IVT</td>
<td>Associated to apoptosis</td>
<td>65</td>
</tr>
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</table>
A similar study on circulating miRNAs in ACM patients with VA was published.68 Yamada et al69 observed higher expressions of miR-144-3p, 145-5p, 185-5p, and 494 in ACM patients with VA compared to healthy controls, IVT patients, and subjects with suspected ACM. Among them, miR-494 seemed to have a central prognostic value because it was linked to recurrent VA after ablation. Moreover, based on in vitro results, a possible correlation between the high expression of miR-494 and the apoptotic process occurring in ACM hearts was proposed despite the role of miR-494 in apoptosis being unclear due to its dual modulation of both anti- and proapoptotic genes.66

Although the interest in circulating miRNAs as disease biomarkers has increased steadily during the last few years, several limitations still hamper their introduction in daily clinical practice. One of the most important issues is the difficulty in standardizing detection and quantification methods.58 Nevertheless, their undisputable potential and the higher sensitivity and specificity in comparison to other biomarker candidates may represent an advantage that can overcome technical issues, thus ensuring their implementation in the clinical setting.

Conclusion
In this review, we summarized several aspects of ACM in relation to blood-based analyses, including genetics, inflammation, and a variety of novel potential circulating biomarkers associated with different ACM features (Figure 1 and Table 1).

Although many of the tests are routinely included in the clinical practice of various diseases, many limitations are still present and need to be addressed before they can be exploited in the ACM field. For example, ACM prognostic specificity and yield in differential diagnosis, both against other arrhythmic or HF diseases and against athletes’ hearts, must be delineated. Many studies have reported that intense training induces the release into the circulation of most of the proposed biomarkers.

The future identification of new ACM-specific biomarkers, either alone or in combination, may overcome the current limitations. In order to achieve this goal, several validation steps for suitable candidates in wide patient cohorts are mandatory to define disease thresholds and admission to clinical practice in order to help patient diagnosis and stratification.

Notably, to date no circulating biomarkers have been proposed in relation to some crucial ACM features, including fibro-adipose substitution. Speculatively, ACM-specific cardiac remodeling may be the source of circulating “debris” that could be exploited as a diagnostic marker. Alternatively, the identification of clinically relevant biomarkers using hypothesis-generating “omics” approaches could provide new hints about unexplored ACM mechanisms and therapeutic targets.

The current knowledge of circulating factors in ACM blood is limited, and clinical application is restricted to genetics and a few HF biomarkers (Table 1). Further research will improve the use of noninvasive blood tests in patients with ACM.

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Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2018.09.023.

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