

Paul Cremer, MD ([00:17](#)):

Hello and welcome to the American Heart Association's recurrent pericarditis podcast series. This is episode five, Pathophysiology of Recurrent Pericarditis. I'm Dr. Paul Cremer. I'm a cardiologist and a cardiovascular imager at the Cleveland Clinic where I'm the associate program director of our cardiac intensive care unit and our cardiovascular medicine training program. I'm also an associate editor for Circulation Cardiovascular Imaging. And it's my privilege today to be joined by two experts in the field of pericarditis, Dr. Aisha Siraj. Dr. Siraj is an assistant professor at Case Western Reserve University, a MetroHealth Medical Center. She received her medical degree from Jinnah Sindh Medical University in Karachi, Pakistan, and completed internal medicine training at Bronx-Lebanon Hospital in New York and her cardiology and her interventional cardiology at the University of Arkansas for Medical Sciences in Little Rock.

Paul Cremer, MD ([01:13](#)):

She's currently the cath lab director, and her interest are related to revascularization in myocardial infarction and post-myocardial infarction complications, including pericarditis. And we're also fortunate to have Antonio Abbate. Dr. Abbate is professor of medicine at the Virginia Commonwealth University in the Pauley Heart Center, but will actually be transitioning to the University of Virginia in the Berne Cardiovascular Research Center, starting in early July. Dr. Abbate received his medical degree from the University Campus Bio-Medico in Rome, Italy, and clinical training in cardiovascular medicine, as well as a PhD in cellular and molecular cardiology from the Catholic University in Rome, Italy. He then came to the US and did an additional internal medicine training at the Virginia Commonwealth University and joined the faculty in the division of cardiology in 2007, rising to the rank of professor of medicine with tenure in 2020.

Paul Cremer, MD ([02:07](#)):

Dr. Abbate is a physician scientist with a distinguished portfolio of investigations in preclinical and translational research in the field of cardio immunology. He's authored more than 400 peer-reviewed publication and served as the principal investigator on numerous clinical trials with an area of research focus related to interleukin-1 as a mediator disease and acute myocardial infarction, heart failure, and of course, pericarditis. I think for us as cardiologists, it's useful to kind of take a step back and maybe have a brief refresher on the immune system. Generally, we think about innate immune response versus adaptive immunity. So, maybe just talk a little bit about that distinction between innate and adaptive immunity, realizing that a lot of cardiologists haven't really thought about this since their medical school days

Antonio Abbate, MD ([02:53](#)):

Sure. Brings back to medical school, although a lot of things have changed since then and as brief concepts, the innate response is that immediate available response that cells have ready to response to the intruders to pathogens, usually viruses, microbes, bacteria. And now we think about COVID, that don't require learning from our immune system and respond in a more stereotyped way, independent on what the insult or trigger is. And of course, this is essential for survival, and it allows to recognize when the danger or the intruder occurs. But what we learn is that sometimes this response can be outrageous and excessive and part of the disease. And we also learn that sometimes this response can be not due to a pathogen or intruder, but to some other danger signals.

Antonio Abbate, MD ([03:58](#)):

And so this is part of what we say our innate response. The adaptive is something that came later in the evolution and it's more fine tuned. It's something that involves the lymphocytes, which is a specialized cell of the white blood cells that has the ability to recognize special motives or antigens, and then create a response that is tailored and aimed at the distinct pathogens. And so, rather than creating an indistinct response that is generalized, is now killing the pathogens in a refined way. As you know, we're [inaudible 00:04:41] living in the world of COVID is more, what is in the world of vaccines or antibodies. And maybe I stop here. So have Aisha, develop on this. Tell us more.

Aisha Siraj, MD ([04:52](#)):

Yes. It brings back exactly to our med school refreshing memory. So just innate, for everyone, if you go back as what Antonio said, it's just a protection that is generally offered by the skin, mucus membranes, preformed immune cells, some proteins. It's pretty fast, and it's the first line of response. Whereas, adaptive is something which is based on an antigen or it's active versus passive. So, active is like what we've done so far, learning like vaccinations and passive can be transferred when the baby is in the womb and having antibodies from the mother or the breast feed. So, those are kind of passive adaptive immunities that we develop over time. Yes, it can go outrageous and it can have detrimental effects if it goes outrageous.

Paul Cremer, MD ([05:38](#)):

Yeah, that's excellent. I think that's a very helpful framework for thinking about a lot of human diseases and we'll focus in a moment on pericarditis, but first maybe elaborate a little bit for us, the distinction between systemic autoimmune diseases versus autoinflammatory diseases in terms of what kind of categories are these, how are they mediated? And maybe just give some examples of each to provide some perspective for our listeners.

Antonio Abbate, MD ([06:06](#)):

Yeah. When you talk about medical school, some of these terminologies were not available when I went to medical school and the terms of autoinflammatory disease is something that has evolved more recently. So, I will maybe start a... Paul, if you allow me, we'll start with the concept of autoimmune disease that has been identified longer ago or more decades ago, where it's a condition where the adaptive immune response has gone awry, and it's now responding to an antigen or a protein that is part of self. And so the disease now is caused by the T-cells or the lymphocytes that are now injuring organs or tissues that shouldn't be injured because they're not part of the offenders. And so, this can be caused by different mechanisms, but now requires too many ways reduce or silence these cells in their response. And autoinflammatory is kind of evolved later when the clinicians realized that not all the inflammatory diseases were caused by this autoimmune response, or this lymphocyte T-cell response or B-cell response, but it was more a normal response of the innate system, innate immune response system, as we were talking earlier.

Antonio Abbate, MD ([07:37](#)):

Now, as I said, this terminology of autoinflammatory response is more recent, but the conditions have actually been known for centuries. And so the periodic fevers, like the familiar Mediterranean fever is an example of autoinflammatory condition or disease is a condition where recurrent inflammatory flares or chronic inflammatory conditions occur not due to an autoimmune response, but to a dysregulated production of the cytokines that are elevated in circulation, mediate fever, and other inflammatory responses due to an abnormal regulation of the innate system. And of course, we could go on to talk

about these two systems for hours, but I think broadly speaking, the autoinflammatory is the innate system that is dysregulated and the autoimmune is the adaptive system that is dysregulated and responding to self.

Aisha Siraj, MD ([08:41](#)):

Exactly, Antonio. So, that brings us to our topic today for pericarditis and recurrent pericarditis, that highlights the importance of both the pathways, because it can be due to systemic autoimmune or autoinflammatory. So, both mechanisms can be involved in the topic that we are going to be discussing forward, and it can be due to adaptive autoimmune hypothesis behind it, or maybe autoinflammatory, and we will dig down more into this topic, but as you said, it can be a dysregulation that can lead to a cascade of events in a person.

Antonio Abbate, MD ([09:17](#)):

Yeah, and makes me think of how much progress has been made in this field. How many Nobel prizes have been awarded in the past decades about the immune system and how the pathogens and danger is recognized, how the cells communicate with each other in using humoral or soluble mediators like cytokines, like interleukin-1, or how specialized cells are involved into the immune response. And this has been clarified in the past decades and has led the way to a better understanding, not only of the autoinflammatory and autoimmune diseases, but it has also opened the way to the treatment of organ transplantation and other conditions.

Paul Cremer, MD ([10:10](#)):

Excellent. I think as was noted, there is a lot of overlap within specific diseases. Certainly there's prototypical autoinflammatory diseases, inherited conditions like familial Mediterranean fever that Antonio highlighted, but I think it is useful for us as cardiologists to appreciate this distinction between the innate immune response and predominantly autoinflammatory disease, versus adaptive immunity and autoimmune disease. And I think as Aisha touched upon that, that brings us to the topic of today in terms of pericarditis. So, what are some thoughts in your view in terms of the understanding of the underlying immune mechanisms for different types of pericarditis?

Antonio Abbate, MD ([10:52](#)):

So, as already introduced by Aisha, pericarditis, which is broadly defined by the inflammation of the pericardial sac, may be secondary to many causes. And this is related both to what we've been talking about as autoinflammatory mechanisms or autoimmune mechanism. And in terms of the autoinflammatory mechanism, that make the inflammation persistent, is when there are triggers that allow the immune cells, the white blood cells to be triggered, inflamed, activated, by a variety of stimuli like viruses or trauma, like blood during a procedure, like an ablation procedure. And that stimulates the cells to produce cytokines primarily into interleukin-1, alpha or beta, that make the pericardial cells inflamed, produce secondary mediators and make the pericarditis in some way persist.

Antonio Abbate, MD ([11:59](#)):

And these are the more common forms of pericarditis. Sometimes the cause is not immediately identifiable because the virus is not immediately identifiable. Sometimes we refer to this as postviral or idiopathic. Some other times the cause is more easily identifiable because there's a procedure related to it. And these represent likely 70% of the cases of pericarditis. In other cases, as we were referring earlier, the patients has an underlying autoimmune form of disease like systemic lupus erythematosus

or rheumatoid arthritis, where there is considered to be an abnormal response to an antigen or trigger. And the disease is more persistent on the base of abnormal T or B-cell response.

Aisha Siraj, MD ([13:00](#)):

Exactly, Antonio. So, for the audience here, just to break it up, that most of when we talk about pericarditis, is idiopathic 70, 90% of the cases are idiopathic. It can be infectious and non-infectious including viral bacterial. It can be fungal. Other autoinflammatory can be uremia. For instance, we see a lot in the post-MI we see both innate and adaptive immunity. When we talk about post-MI pericarditis, whether it's in the immediate myocardia infarction period, or later on presenting as Dressler's syndrome. It can be due to any malignancy. We've seen that evolving postcardiac surgery are some of the causes. Anytime you've had mediastinal irradiation or anything can cause... and both pathways evolve side to side in many of these causes of pericarditis.

Paul Cremer, MD ([13:51](#)):

Yeah, I think that's great. And it really ties into the triggers of pericarditis, especially with recurrences, which you both touched upon. There can be an initial insult, with the acute episode, be it a viral infection or postcardiac injury syndrome, sort of trauma or blood that enters the pericardium. In developed world, that would be the two most common causes. And it does seem to be a subset of these patients, unfortunately, who develop recurrences. And I would say more and more, it seems that recurrent process, as we've been touching upon is driven by an exuberant, if you will, autoinflammatory response.

Paul Cremer, MD ([14:31](#)):

And sometimes it may be identifiable to another viral infection or the patient can tell you that there was a specific trigger. And they know that every time I do this kind of activity or too much, it brings it on. But oftentimes it's difficult to identify and we don't know. So, I think there's still a lot to learn, but also say that no conversation about the innate immune response should go on without touching upon the inflammasome. So maybe we haven't yet spoken some about cytokines in particular, the apical cytokine of innate immune response interleukin-1, but where does the inflammasome fit into all of this innate immune response?

Aisha Siraj, MD ([15:08](#)):

So, inflammasomes are stimulus induced cytoplasmic multimeric protein complexes. They're components of innate immune system. And they play a very major role in inflammation. What they do is they activate these molecular platforms that are activated upon cellular infection or stress that triggers the maturation of these pro-inflammatory cytokines, such as we talk about interleukin-1, [inaudible 00:15:37] factor, and they then engage the immune defenses. They can actually have an overwhelming production of pro-inflammatory cytokines and recruitment of more immune cells, like neutrophils, monocytes, and all these cells. So, inflammasomes play a major role in when it comes to talking about inflammation in the innate immune system.

Antonio Abbate, MD ([16:02](#)):

Definitely. As Aisha has pointed out, the inflammasome is very central to this response to tissue injury. And Paul, as you hinted, the injury can be from a viral infection or a bacterial infection, less common here in the Western world, but can be traumatic from blood in the pericardial space. That's a space where blood shouldn't be. And as Aisha explained very clearly, the inflammasome amplifies the

response by creating a large amount of cytokines and especially recurrent pericarditis is really a failure to resolve that initial inflammatory response that can be partially normal to repair the damage, but that inability to resolve and this amplified response becomes the cause of the disease and becomes the basis of the autoinflammatory syndrome. And the reason did we know this is from the successes of the inflammasome targeted or inflammasome based therapies like colchicine or IL-1 based therapies, that have shown to really quench this inflammatory response and the syndrome of pericarditis.

Paul Cremer, MD ([17:22](#)):

Yeah, that's great. And I do want to get into the therapies and their mechanism of action and how it may interplay with the pathophysiology we've been discussing. But first I wanted to spend another moment on interleukin, maybe an area that we need further research, but the distinction between interleukin-1 alpha and interleukin-1 beta. Interleukin-1 alpha potentially acting as an alarm, whereas interleukin-1 beta is secreted more systemically. So, maybe touch upon that a little bit. And I think a practical question that I sometimes get related to that is, how do we measure and track inflammation in these patients? And I'm sure you guys have been asked these questions before is like, "Can we check interleukin-1 levels..." Which at least my understanding, and you guys can correct if I wrong, "Is that for clinical purposes?" No. And some of the therapies may actually not change the IL-1 levels, but maybe talk about how one, is there anything to this distinction between IL-1 alpha and beta, and what do we still need to learn? And two, how are you tracking the inflammatory response in your patients clinically?

Antonio Abbate, MD ([18:23](#)):

Yep. Maybe I could start with the alpha and IL-1 beta. They both come from a gene that is presumably been a duplication of the same gene in the development of the species. And the difference is that the IL-1 alpha lacks the sequence that then is processed from caspase-1. And so, IL-1 alpha really becomes a pro-cytokine that is not processed and released outside the cell, if not in very small amounts, but it is released when the cell is injured. And it also has a role in the membrane expression. But for the large part, the IL-1 alpha works as you mentioned, Paul, as an alarm and when it is released, it is a sign of cellular injury. It is expressed more in cells of epithelial and mesothelial origin. And so it's telling the organ, that there's something that is being damaged and that should trigger, now the IL-1 response that also feeds more IL-1 and the inflammasome activation. This is something we've learned from Charles Dinarello and Peter Libby many years ago.

Antonio Abbate, MD ([19:40](#)):

And IL-1 beta is again, similar family, but it does have that caspase-1 processing sequence and therefore is rapidly cleaved in the inflammasome and also is expressed in high amount in monocytes, in other leukocytes. And so it's produced in high levels. And so, if we were to try to measure IL-1, we would be measuring IL-1 beta. That's why, when IL-1 was cloned, it was actually IL-1 beta that was cloned, not IL-1 alpha, because it was the most circulating form and that's the fever molecule, but you are right. IL-1 beta is not a real good biomarker and I'll rapidly share my practice. And I'll be interesting to see what Aisha does in her practice. But I actually think that C-reactive protein is a reasonable biomarker because it's readily available in every lab. Has a long half life and it correlates with IL-1 activity. So, I don't usually use other cytokines and just relate to this available biomarker. But what is your practice Aisha?

Aisha Siraj, MD ([20:53](#)):

So exactly the same. It's very difficult actually, in clinical practice. That's what Paul and you pointed out, that we don't measure them. Yes, of course, if you're in a lab and you are working on these specific

targets, you can measure them and see their response and response of the medicines that you're working with. But in real life practice, we take CRP as a marker for inflammation. You've already mentioned that IL-1 is stored actually in healthy cells and it's only excreted when the damage has occurred or some trigger has happened. On contrary IL-6 is something that is produced by the inflammatory leukocytes. And then it facilitates infiltration of monocytes, neutrophils, macrophages, and then it amplifies the response and it activates much more down line if you see cyclooxygenase and stuff like that, which enhances the inflammatory process. But unfortunately in today's day and age, we don't have... clinically, we cannot measure or monitor them and cannot redirect our therapies based on measuring in a human population. But yes, in our setting also we do the same. We go by C-reactive protein and measure ESR for signs of inflammation.

Paul Cremer, MD ([22:05](#)):

Absolutely. I think we're all on the same page and my answer as well, when I have that question is that the C-reactive protein is really the biomarker of choice in this clinical setting and to have insight into the innate immune response. So, maybe if you both could touch upon the drugs that have proven to be efficacious in pericarditis and how they relate to some of the pathophysiology, we've been talking about.

Aisha Siraj, MD ([22:29](#)):

Some of the drugs that we use, and since we are talking about recurrent pericarditis, we have to keep in mind, what are the mechanisms of recurrent and pericarditis, are we looking into when targeting these therapies? Is it reactivation of something which is dormant like body particles? Is it transformation of self antigens? Is it the production of autoantibodies? So, looking at the etiology is really important because it really has an impact on morbidity. Recurrent pericarditis actually carries a very significant morbidity to the patients that I've seen in my clinical practice currently. When we are talking about targeted drug mechanism much has been done on it. And still it's an area where work is still on progress. Some of those I would highlight as one of them is colchicine, which is commonly used. Its own effects on the innate immune system, the way it works, it binds to alpha and beta tubulin to create tubulin-colchicine complex, that prevents formation of microtubules.

Aisha Siraj, MD ([23:29](#)):

So, actually these microtubules, this is how they interfere with several inflammatory pathways. Such as adhesion, recruitment of neutrophils, superoxide production, inflammation activation, and so forth, going forward. Others that we look into when we are talking about pericarditis is NSAIDs because we know when an inflammatory cascade has started and we've activated cyclooxygenase. We want to innovate that cyclooxygenase pathway. So, can we innovate prostacyclin and prostaglandin production and control the inflammatory path? The other few things that we look into is steroids. There had... steroids, everybody knows, has an antiinflammatory as well as immunosuppressive, which works for recurrent. Though it has been studied that patients who've been treated on their first episode of pericarditis with steroids, are more likely to have recurrent pericarditis, but sometimes we have these different kind of pericarditis that we've tried everything.

Aisha Siraj, MD ([24:27](#)):

And this is that we have to give to our patients. So, these are glucocorticoid receptor that is located intracellularly within the cytoplasm, and then it binds, translocates rapidly into the nucleus where it affects the gene transcription and causes inhibition of gene expression and translation for inflammatory

leukocytes and structural cells. So, basically it's all immunosuppressive effects going so forth, and so forward then in the current day and age, we have developed something and the research is still ongoing. And I think Antonio can highlight on the interleukin pathways and interleukin inhibitors, if Antonio would like to do that.

Antonio Abbate, MD ([25:06](#)):

Yes. Well, great overview Aisha. And I think to kind of put it together with our introduction of the autoinflammatory versus autoimmune diseases and the concept of persistent inflammation in the biomarkers, this is where the clinical and biomarker picture can help us guide the treatment. And so, the patients that have persistent or recurrent symptoms and have elevated levels of C-reactive protein, are really showing a picture of autoinflammatory condition or syndrome in which blocking the inflammasome or the product of the inflammasome interleukin-1, has shown to change the natural course of the disease. And in those patients, we'll have again, recurrent pericarditis and elevated markers like C-reactive protein treatment with an IL blocker like Riloncept or in another prior trial, with anakinra, which is recombinant to IL-1 receptor antagonist, has shown to significantly prevent the recurrence of the pericarditis.

Antonio Abbate, MD ([26:15](#)):

This is very important to understand, because you are really dampening that autoinflammatory cascade that is triggering the recurrence of the syndrome of the condition there. I liked very much how you went through all the other available treatments for pericarditis. We did talk about autoimmune conditions that can be associated with recurrent pericarditis. I think it's important to note that in that case, pericarditis is one of the manifestation of the autoimmune condition. In that case, you need to treat the entire autoimmune disease. So, if someone has systemic lupus erythematosus with pericarditis, then the treatment is for the lupus and it may involve a treatment that is for the T-cells or the B-cells, not necessarily for the pericarditis alone. In many cases, those patients do not have evidence of inflammation with C-reactive protein elevation, or if it is, it's secondary to the injury, not as a primary cause.

Antonio Abbate, MD ([27:17](#)):

You mentioned colchicine, how critical it is, and it is important to point out that by inhibiting the microtubules, it actually is also inhibiting the aggregation of the inflammasome, which is so critical to that autoinflammatory response in pericarditis. And so, colchicine is now first line in acute and recurrent pericarditis and should be, because likely preventing that first wave of injury may prevent that autoinflammatory response that now promotes recurrent pericarditis. The NSAIDs have considered first line and a mainstay of treatment of pericarditis, but the data to support the treatment, the use of NSAIDs is not very strong. And considering that the cyclooxygenase is to activation and prostaglandin production is really downstream. One should think that is possibly just palliative and blocking that may improve pain, but not necessarily change the course of the disease. And so while you want to do it to improve pain, you should think about using other drug to actually affect the inflammatory response.

Paul Cremer, MD ([28:32](#)):

A great overview, really comprehensive. And I agree. I would emphasize again, that colchicine is going to be the mainstay of therapy for acute and recurrent pericarditis. Certainly, in patients with systemic autoimmune disease, the pericarditis, as you said, as a manifestation of that. And those patients will often be on corticosteroid therapy as well. And then in the patients who have refractory disease, which

we would think of as either colchicine resistant or corticosteroid dependent, recurrent pericarditis. That's where the IL-1 blockers have really been a breakthrough in terms of controlling acute episodes and preventing further recurrence. So, we've really covered a lot of ground in terms of the distinction between the innate and adaptive immune response.

Paul Cremer, MD ([29:21](#)):

Understanding the various triggers that can lead to an acute or recurrent episode of pericarditis, the importance of understanding that trigger to direct further therapy. And I think with an emerging thought that a lot of this is related to inappropriate, innate immune response over production of interleukin-1, inappropriate activation of the inflammasome and some of the therapies that may help our patients who need inhibition of these pathways. This has been a great discussion and to our listeners out there, thanks for joining us and participating in episode five, Pathophysiology of Recurrent Pericarditis. This podcast series on pericardial disease, is supported by an educational grant from Kiniksa Pharmaceuticals and for more educational opportunities, please visit the AHA's website at [learn.heart.org](http://learn.heart.org). Thanks again.