MINERALOCORTICOID RECEPTOR ACTIVATION FOLLOWING ACUTE MYOCARDIAL STRETCH.

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ABSTRACT

Myocardial stretch induces a two-phase increase in developed force. The first phase occurs immediately, is due to an increase in myofilament Ca^{2+} responsiveness, and is the expression of the Frank-Starling mechanism. The second phase, gradually developed, results from an increase in intracellular Ca^{2+} concentration and is known as "slow force response" (SFR) to stretch. Characterization of the subcellular basis of the increase in Ca^{2+} responsible for the SFR development was an important objective of our laboratory group during last two decades. We have compiled enough evidence to suggest that the SFR is the mechanical expression of an autocrine/paracrine loop of intracellular signals leading to the reactive oxygen species (ROS)-mediated activation of redox-sensitive kinases that activate (phosphorylate) the cardiac Na^+/H^+ exchanger (NHE1), increasing intracellular Na^+, and consequently, Ca^{2+} concentration. Recently, we demonstrated that mineralocorticoid receptor (MR) activation after stretch is critical for the progression of this complex signaling pathway. Interestingly, clinical evidence assigns a detrimental role to MR activation in the pathophysiology of heart failure (HF), in which cardiac wall stretch is an important triggering factor. The aim of this mini-review is not only to share our own experience describing novel non-genomic effects of MR activation after acute myocardial stretch and the physiological consequences, but also to discuss other possible pathophysiological implications, as well as the potential clinical impact of this important discovery.

Keywords: myocardial stretch, mineralocorticoid receptor, reactive oxygen species, slow force response.

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Introduction

During last two decades, our laboratory group focused on exploring early intracellular signals triggered by myocardial stretch. We were particularly interested in describing acute intrinsic mechanisms of the heart to adapt cardiac output to changes in hemodynamic conditions, but also to explore its potential pathological consequences if stretch persists over time. A sudden increase in left ventricular end-diastolic volume (wall stretch) caused by either increasing aortic resistance to ejection or venous return, immediately leads to a more powerful contraction. This increase in developed force occurs in two phases: A rapid one that constitutes the well-known Frank-Starling mechanism attributed to enhanced myofilament responsiveness to Ca^{2+}, and the SFR that is gradual and due to an increase in Ca^{2+} transient amplitude. Characterization of the subcellular basis of this increase in Ca^{2+} responsible for the SFR development was the area of research in which we have been working for almost 20 years. We were able to unveil a complex autocrine/paracrine signaling pathway underlying this slow increase in cardiac contractility, that may also be responsible for triggering cardiac hypertrophy (CH) and HF when sustained over time (for review see [1]). Briefly, the mechanism comprises: (1) Stretch-triggered release of Angiotensin II (Ang II)/activation of AT1 receptors, (2) release/formation of endothelin (ET)/activation of ETA receptors, (3) MR activation, (4) transactivation of the epidermal growth factor receptor (EGFR), (5) increased formation of mitochondrial ROS, (6) activation of redox-sensitive kinases upstream NHE1, (7) NHE1 activation, (8) increase in intracellular Na^+ concentration, and (9) increase in Ca^{2+} transient amplitude through the Na^+/Ca^{2+} exchanger. Among our latest contributions to understand this striking signaling pathway, the finding of the critical role played by an increased ROS production[2], together with the demonstration that non-genomic effects of MR activation are essential to trigger these ROS [3, 4], are probably the most important ones. The next sections will mainly focus on our own experience regarding non-genomic effects of MR activation following acute myocardial stretch. We will briefly discuss its physiological and pathophysiological consequences, as well as the potential clinical implications of this important discovery.

Making a long story short

Several years ago, elegant experiments by Cingolani et al [5] in isolated cat cardiomyocytes demonstrated that Ang II, in a concentration that well resembles the physiological one, increased sarcomere shortening entirely through an autocrine crosstalk with endogenous ET. Interestingly, a rise in mitochondrial ROS production accompanied this effect, which was on the other hand cancelled by preventing oxidative stress, clearly revealing a cause-effect relationship. [5] Since we had previously provided evidence that Ang II/AT1 receptor activation constitutes the initial step in the signaling pathway leading to the SFR, we hypothesized that an increase in ROS production could be part of this signaling cascade. Certainly, we subsequently found that the SFR was accompanied by an increased ROS production that promoted NHE1 activation [2]. Conversely, the suppression of ROS production by either scavengers or inhibitors of its formation cancelled the SFR, [2], once again unveiling a cause-effect relationship. Consistently, we demonstrated that stretch stimulated the redox-sensitive kinase cascade of ERK1/2-p90RSK increasing its phosphorylation level, effect that was suppressed by AT1-receptor blockade with losartan. We were also able to demonstrate the mitochondrial origin of ROS that were triggered by a small amount of NADPH oxidase-derived ROS, [2], in a mechanism that clearly reminds the so-called “ROS-induced ROS-release” phenomenon described by others. [6, 7].

The question regarding to the reasons for exploring the putative activation of MR following myocardial stretch may be certainly asked. Two lines of existing evidence induced us to investigate the possible participation of the MR in the signaling cascade leading to the SFR development: (**1)** The confirmed link between Ang II-AT1 receptor and the MR, [8-10] (**2)** The fact that EGFR transactivation (that is part of the route leading to the SFR [11, 12]) can be triggered by MR activation. [8, 13, 14]. We initially demonstrated that MR activation is necessary to promote ROS formation by a physiological concentration of Ang II, since the effect was cancelled by blocking the MR with spironolactone or eplerenone.[3] As expected, the increase in ROS production was cancelled by antagonizing AT1 receptors, but also by ET1 (type A) receptor blockade, by preventing EGFR transactivation, by inhibiting NADPH oxidase, or by targeting mitochondria, while it was unaffected by glucocorticoid receptor (GR) inhibition. [3]. Interestingly, an increased ROS production promoted by an equipotent dose of aldosterone (ALD) was prevented by blocking the MR (eplerenone), but not by inhibiting GR or protein synthesis, suggesting that it was a specific and non-genomic MR effect. [3] On the other hand, ALD also increased the phosphorylation level of the redox-sensitive kinases ERK1/2-p90RSK, and the NHE1, effects that were all eliminated by eplerenone or by preventing EGFR transactivation. [3] We subsequently proved the cancellation of the SFR either by pharmacological MR blockade [3] or the specific silencing of MR expression (interference RNA), [4] but not by GR blockade or protein synthesis inhibition. [3]. Taken together, these results clearly demonstrated that post-stretch MR activation is crucial to trigger mitochondrial ROS formation leading to NHE1 activation, and hence, to the development of the SFR. **Figure 1** summarizes the most representative findings that support our conclusions, by compiling original force records of isolated papillary muscles subjected to a sudden increase in length under four different experimental conditions. While the "upper left" panel shows the classical force response to stretch consisting of an initial rapid phase followed by the SFR, the other panels show the cancellation of the SFR by silencing MR expression, preventing mitochondrial ROS formation, or silencing NHE1 expression. For a better comprehension of the complex sequence of events triggered after myocardial stretch, see the scheme depicted in **Figure 2**.

MR activation in the myocardium: Facts and doubts

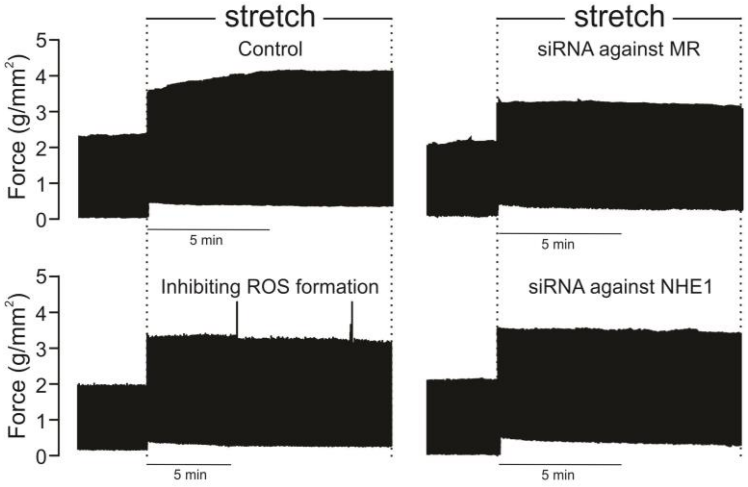

Figure 1. Original force records of isolated papillary muscles subjected to a sudden increase in length under different experimental conditions. **Upper left** ("control"): Classical two-phase force response to stretch consisting of an initial rapid one followed by the SFR. **Upper right**: Cancellation of the SFR in muscles with silenced MR expression. **Bottom left**: Cancellation of the SFR by preventing mitochondrial ROS formation. **Bottom right**: Cancellation of the SFR in muscles with silenced NHE1 expression. (Adapted from: *Pérez NG et al. J. Appl. Physiol. 111[3]: 874, 2011 -upper left and bottom right-, Díaz RG et al. Hypertension 63: 112, 2014 -upper rigth-, and Caldiz CI et al. J. Physiol. 584.3: 895, 2007 -bottom left-*).

In order to better comprehend the possible role played by the MR in cardiac physiology/pathophysiology, it is important to clarify some general aspects concerning the receptor activation. The MR is a member of the steroid/thyroid hormone receptor superfamily of ligand-inducible transcription factors that mediates classic ALD effects. Although the increase in ALD concentration constitutes the best-recognized stimulus to MR, it can be also activated in normal or even low-ALD states. [15, 17] Moreover, the MR was shown to have equivalent high affinity for ALD, cortisol and deoxycorticosterone. [18] This is extremely important since circulating glucocorticoid levels are greater than those of ALD determining that MR are usually occupied, but not activated, by glucocorticoids. However, under pathological conditions and increased oxidative stress glucocorticoids have been shown to activate the MR.[19] Interestingly, in epithelial ALD-target cells, the highly expressed 11β-hydroxysteroid dehydrogenase enzyme (11βHSD2) facilitates ALD occupancy and activation of the MR, by converting active glucocorticoids (e.g. cortisol) into receptor-inactive 11-keto analogs (e.g. cortisone), significantly reducing intracellular glucocorticoid levels (to ~10-fold those of ALD).[20-22] In contrast, in non-epithelial tissues such as hippocampus, vascular smooth muscle, fat or the myocardium (of particular interest for us), the expression of 11βHSD2 is too low to prevent cortisol access to the MR in competition with much lower concentrations of ALD. Therefore, the question as to how ALD can occupy and activate the MR in tissues with very low expression of 11βHSD2 as the myocardium is still unanswered. However, in light of our recent findings, the activation of the MR following myocardial stretch appears unquestionable.[3, 4] In this context, it seems reasonable to consider any of the following possibilities for ALD-independent MR activation: (**1**) Glucocorticoid-mediated MR activation, especially under conditions of enhanced ROS production, as reported by Mihailidou et al.[23] (**2**) ligand-independent MR activation as the redox-sensitive Rac1-dependent activation proposed by Nagase et al.[23] (**3**) Direct MR phosphorylation independent of its own ligand, as proposed by Kato et al.[24] for the estrogen receptor. (**4**) Specific changes in MR conformation induced by strain, as proposed by Zou et al. [25] to explain AT1 receptor activation by mechanical stretch. In summary, we have provided enough evidence to state that activated MR is required for the effect of stretch on cardiac force. Unfortunately, whether the mechanism involves an autocrine/paracrine effect of ALD, or an ALD-independent pathway remains to be elucidated.

Physiological and pathophysiological consequences of myocardial MR activation. Potential clinical implications.

Physiologically, the SFR constitutes a powerful mechanism occurring just after the Frank-Starling mechanism took place by which the heart adapts to an abrupt increase in afterload. However, crucial events leading to the increase in intracellular Ca^{2+} concentration responsible for the SFR development (AngII/ET release, MR activation, increased oxidative stress and NHE1 hyperactivity, **Figure 1 and 2**) are also critically involved in the progression of pathological CH and HF (for review see [26, 28]). In this context, it is attractive to hypothesize that mechanical stress may not only trigger immediate intrinsic heart mechanisms to adapt cardiac output to changes in hemodynamic conditions, but also constitutes the first step toward pathologic cardiac remodeling if the initial events are sustained over time (chronic wall stretch). CH and HF are two of the most important health problems in western societies. Current treatment against these pathologies is primarily based on preventing the action of hormones including AngII, catecholamines and ALD. Regarding ALD antagonism, the widely used term

"ALD inhibition" should be replaced by "MR antagonism", since as stated before, experimental evidence demonstrated that ALD is not the only agonist binding to and activating the MR. [19]

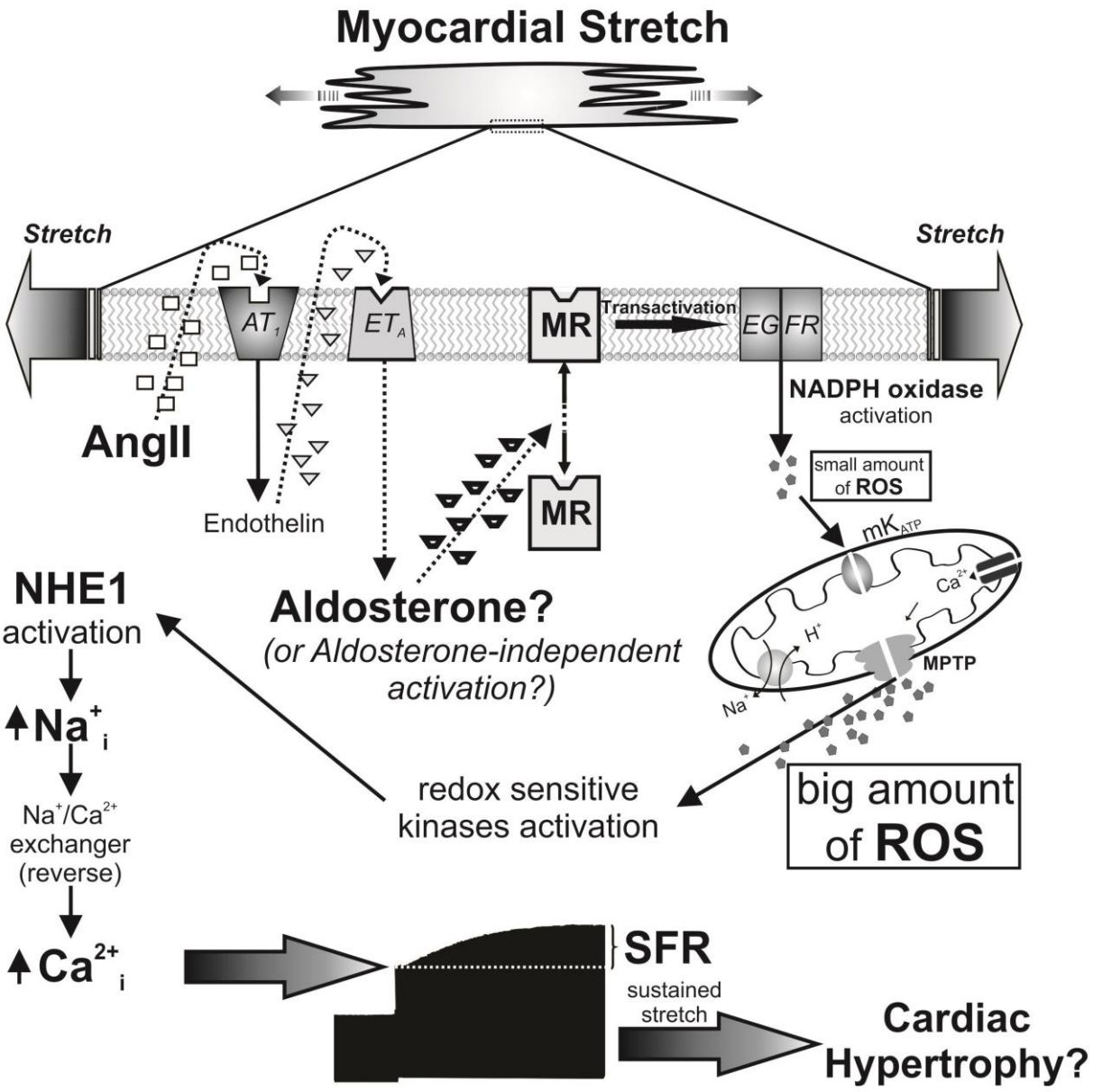

Figure 2. Schematic representation of the intracellular sequence of events triggered by myocardial stretch.

The striking benefits of MR antagonists in HF patients have been demonstrated by several studies. The first MR antagonist accepted for clinical use in humans was "spironolactone", which despite some tolerability problems was approved to be tested in patients with severe HF (Class III-IV of the New York Heart Association "NYHA") in the **RALES** (Randomized Aldactone Evaluation Study) clinical trial. An interim analysis revealed a ~30% reduction in the relative risk of death in spironolactone-treated patients, [19] together with an equal and impressive reduction in hospitalization for cardiac reasons. This excellent prove of efficacy of

MR antagonism provoked a premature termination of the trial. Afterward, the **EPHESUS** (Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) clinical trial tested the effect of eplerenone, a more specific MR antagonist, in patients with acute myocardial infarction with left ventricular systolic dysfunction. Treatment started 3 to 14 days after infarction and was maintained during 16 months, revealing a reduction of ~15% in all-cause mortality and ~21% in sudden cardiac death. [30] More recently, the effect of eplerenone in patients with less severe HF was proved in the **EMPHASIS-HF** (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) clinical trial. This study enrolled patients with HF class II-III of the NYHA and left ventricular ejection fraction of no more than 35%. Once again, the study was stopped prematurely due to the outstanding benefit obtained by eplerenone therapy in terms of reduction of cardiovascular death risk and hospitalization. [31] The treatment was then extended to both arms of the trail.

In contrast to the beneficial effects observed in the three previous clinical trials, in the **TOPCAT** (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) study, spironolactone failed to improve clinical outcomes in patients with symptomatic HF and relatively preserved ejection fraction (≥45%). [32] Researchers argued that since the study enrolled patients from six different countries, regional heterogeneity of practice patterns and/or accuracy of diagnosing methods to identify this subgroup of HF patients might have conspired to reach reliable results. In fact, they could observe beneficial treatment effects in patients coming from American countries that were not observed in those from Russia and Georgia.

The most recent one is the **ALBATROSS** (Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up) study. It failed to show benefits of early MR blockade (single intravenous bolus of potassium canrenoate followed by oral spironolactone for 6 months) in patients admitted for myocardial infarction irrespective of the presence of HF or left ventricular dysfunction. [33]

The results of the last two clinical trials clearly limit general conclusions about the effects of MR antagonism in cardiac pathologies. However, the methodological uncertainties associated with **TOPCAT,** and the completely different target population enrolled for **ALBATROSS** at least invite us to propose separated conclusions. On the one hand, while clinical evidence appears to undoubtedly demonstrate beneficial effects of MR blockade in patients with severe HF, further investigation is needed to precisely clarify its role in those patients with relatively preserved ejection fraction. On the other, the treatment clearly lacked of benefits when applied just after myocardial infarction irrespective of patient's ventricular function.

Beyond these controversies, the mechanisms by which MR antagonism provide cardiovascular protection in certain group of HF patients are not completely understood, and the clinical use of these compounds remains lower than expected. In this context, the demonstration in our basic research studies that MR activation after acute myocardial stretch is a crucial early signal to the development of the SFR may shed some light to understand the role of MR activation in cardiac pathophysiology. In this regard, it is tempting to suggest that prevention of oxidative stress with the consequent prevention of NHE1 activation should be considered as a potential key factor for the salutary effects of MR antagonism in humans.

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