


Review

# MicroRNAs Regulating Renin–Angiotensin–Aldosterone System, Sympathetic Nervous System and Left Ventricular Hypertrophy in Systemic Arterial Hypertension

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**Abstract:** MicroRNAs are small non-coding RNAs that regulate gene and protein expression. MicroRNAs also regulate several cellular processes such as proliferation, differentiation, cell cycle, apoptosis, among others. In this context, they play important roles in the human body and in the pathogenesis of diseases such as cancer, diabetes, obesity and hypertension. In hypertension, microRNAs act on the renin–angiotensin–aldosterone system, sympathetic nervous system and left ventricular hypertrophy, however the signaling pathways that interact in these processes and are regulated by microRNAs inducing hypertension and the worsening of the disease still need to be elucidated. Thus, the aim of this review is to analyze the pattern of expression of microRNAs in these processes and the possible associated signaling pathways.

**Keywords:** microRNAs; hypertension; renin–angiotensin–aldosterone system; sympathetic nervous system; left ventricular hypertrophy

## 1. Introduction

Systemic arterial hypertension (SAH) is a multifactorial disease that is associated with genetic factors, such as inherited genes that favor increased blood pressure and environmental factors, including hypersodic and hypercaloric diet, overweight and obesity, physical inactivity, alcohol consumption in excess, advanced age, among other factors [1]. SAH is also defined as a chronic state of high blood pressure levels [2].

It is estimated that the global prevalence of SAH is greater than 30% in individuals aged 20 years or more. This rate varies when analyzed separately in some countries, with the percentage difference being almost 5% higher in medium- and low-income economy countries when compared to high-income economy countries [3]. In addition, it is known that the SAH is also associated to the development of type 2 diabetes and other comorbidities.

Several processes are associated with increased blood pressure levels and later with SAH, including: changes in the renin–angiotensin–aldosterone system (RAAS), activation of the sympathetic nervous system (SNS), endothelial dysfunction and increased oxidative stress [4]. These long-term pathophysiological processes result in hemodynamic pressure overload promoting cardiac remodeling and pathological cardiac hypertrophy in SAH [5].

Little is known, however, about the molecular mechanisms that initiate and govern these pathophysiological processes in SAH, which begin to be elucidated through microRNAs (miRNAs). MiRNAs are small ribonucleic acids (RNAs), non-coding RNA and gene expression regulators at the post-transcriptional level [6], their function is to degrade or inhibit one or several target messenger RNAs [7,8].

Some studies have reported miRNA deregulation in SAH, promoting activation of RAAS and SNS [9], and inducing pathological cardiac hypertrophy of the left ventricle [10]. However, the molecular mechanisms regulated by miRNAs that regulate the RAAS, SNS and left ventricular hypertrophy (LVH) in SAH still need to be elucidated. Thus, the aim of this review is to analyze the expression of deregulated miRNAs in RAAS, SNS and LVH in SAH, including possible signaling pathways associated with these processes.

## 2. MiRNAs and Activation of the Renin–Angiotensin–Aldosterone System in SAH

The renin–angiotensin–aldosterone system (RAAS) is of fundamental importance in the control of extravascular volume and blood pressure [11]. Due to its regulatory role, RAAS inhibition has therapeutic implications for several chronic diseases, such as SAH, type 2 diabetes and heart failure [12].

Renin is an enzyme synthesized by the juxtaglomerular cells of the kidney and stored in its inactive form as prorenin [13]. In situations of blood pressure drop, circulating volume depletion, reduced serum sodium concentration and sympathetic activation, prorenin molecules will be cleaved and renin will be released, which will act as the main regulator of RAAS [14].

Angiotensinogen is a circulating protein, synthesized by the liver, which will be metabolized under the action of renin, forming angiotensin I, a peptide. The conversion of angiotensin I (Ang-I) to angiotensin II (Ang-II) occurs mainly through the action of the angiotensin-converting enzyme (ACE) in the pulmonary microcirculation [15].

Angiotensin II acts by stimulating the type 1 angiotensin II (AT1R) receptor, causing vasoconstriction in the cardiovascular system, reducing the excretion of sodium and water, stimulating the synthesis of aldosterone, a mineralocorticoid synthesized in the glomerulosa of the adrenal cortex, among other functions [12,16]. Aldosterone also modulates circulating volume through marked stimulation of sodium reabsorption at the level of the renal tubules, with consequent fluid retention, in addition to potassium excretion [14,16].

RAAS imbalances contribute to the development of SAH, due to frequent and intense vasoconstriction of arterioles that cause an increase in peripheral vascular resistance and subsequently in blood pressure, in the long term, target organ damage occurs with more serious consequences [11,17].

Many miRNAs regulate RAAS genes. MiR-27b and miR-145 attenuate angiotensin converting enzyme-1 (ACE-1) expression, but these miRNAs are downregulated in hypertension, increasing ACE-1 expression [18,19]. MiR-143 and miR-421 are overexpressed in hypertension, targeting angiotensin converting enzyme-2 (ACE-2) and contributing to increased blood pressure [19,20].

MiR-483 targets multiple RAAS genes, such as angiotensinogen (AGT), ACE-1, ACE-2 and angiotensinogen receptor 2 (AGTR2), however, the expression of miR-483 is downregulated in vascular smooth muscle cells (VSMCs) stimulated with Ang-II, which leads to overexpression of its target genes and vascular hypertrophy [21]. MiR-143/145 cluster also regulates ACE-1, and when these miRNAs are poorly expressed in VSMCs, it promotes an increase in ACE-1 expression, inducing a reduction in its contractile phenotype and vascular dysfunction [22].

In this context, VSMCs stimulated with Ang-II present reduced miR-155 expression and increased AT1R expression, leading to increased cell proliferation, however, the increase in the expression of this miRNA can abrogate this effect [23]. Likewise, another miRNA, miR-130, was overexpressed, reducing the expression of the target gene GAX, contributing to the proliferation of VSMCs when stimulated with Ang-II [24]. MiR-27a also had its expression elevated in VSMCs stimulated with Ang-II, reducing the expression

of  $\alpha$ -smooth muscle-actin ( $\alpha$ -SMA), leading to proliferation and migration of VSMCs, promoting change in contractile phenotype and reduction in vascular function [25], which favors an increase in peripheral vascular resistance and consequently induces an increase in blood pressure.

In Ang-II-stimulated rat aortic adventitial fibroblasts, miR-122 was overexpressed, decreasing the expression of sirtuin (SIRT-6), elabela (ELA) and ACE-2, promoting reduced autophagic flux and increased cell migration, oxidative stress, inflammation and apoptosis, leading to vascular remodeling [26]. Another miRNA that regulates the apoptosis process in hypertension is miR-133a. This miRNA targets the prorenin receptor (PRR), and in Ang-II-stimulated human umbilical vein endothelial cells (HUVECs) miR-133a was downregulated, increasing PRR expression, which will exacerbate the signaling pathway of the RAAS, promoting apoptosis [27].

In cardiac fibroblasts treated with Ang-II, miR-125b, miR-132 and miR-146b are overexpressed, inhibiting the target genes MMP9 and MMP16, while other miRNAs are downregulated, such as miR-181b, miR-204 and miR-300, increasing the expression of TIMP3 promoting fibrosis in these cells [28].

In another study with Ang-II-stimulated cardiac fibroblasts and HEK293N cells, four miRNAs were found to be overexpressed: miR-29b, miR-129, miR-132 and miR-212, activating  $G\alpha_q/11$ , the extracellular regulated kinase1/2 (ERK-1/2) and AT1R, and the activation of this pathway can promote increased blood pressure [29]. MiR-132/212 cluster is overexpressed in the heart, aorta, kidney and blood circulation of Ang-II-induced hypertensive rats, as well as in the arteries of hypertensive patients, inducing endothelin receptor activation and cardiac hypertrophy [30]. It has also been shown that miR-132 regulates plasma renin levels by modulating blood pressure [31].

In hypertensive rats, miR-16 is overexpressed, reducing the expression of the vascular endothelial growth factor (VEGF), promoting an anti-angiogenic effect, and miR-21 is also highly expressed decreasing the expression of the anti-apoptotic Bcl-2, inducing apoptosis. On the other hand, in this same study, miR-126 is downregulated by increasing the expression of the phosphoinositol-3 kinase regulatory subunit 2 (PI3KR2) which negatively modulates the VEGFR, mitogen activated protein kinase (MAPK) and phosphoinositol-3 kinase (PI3K) signaling pathways, generating microvascular rarefaction in hypertension [32].

Microvascular rarefaction is a process that occurs in individuals with SAH that decreases blood flow in skeletal muscle capillaries, inducing an increase in total peripheral resistance, generating an increase in blood pressure. This process promotes changes in the expression of several miRNAs that regulate vascular remodeling in SAH, being an important factor to be analyzed in future studies for reverse modulation of these miRNAs in an attempt to attenuate this process [33].

Clinical studies also show changes in the expression of miRNAs in hypertensive patients. MiR-136 is downregulated in the serum of patients with hypertension and is associated with elevated levels of RAAS biochemical markers [34]. However, miR-202 is overexpressed in the blood of hypertensive patients, by reducing the receptor soluble (sST2), being associated with high levels of Ang-II and vascular inflammation [35].

Other miRNAs are also with high expression in hypertensive patients, such as miR-21, miR-126, miR-196a and miR-451, while others are with reduced expression, such as miR-181a, miR-638 and miR-663. It was even evidenced that miR-181a and miR-663 target the renin gene, demonstrating that these miRNAs potentially regulate blood pressure [36].

Another miRNA that regulates the renin gene is miR-25. This miRNA is downregulated in the serum of hypertensive patients, elevating the renin expression, promoting RAAS activation and consequently leading to hypertensive heart disease [37]. MiR-155 is also downregulated in the plasma of hypertensive patients, increasing AT1R expression, activating the RAAS signaling pathway, increasing blood pressure [38] (Table 1).

**Table 1.** Expression of miRNAs in RAAS, SNS and LVH.

MicroRNAs in RAAS, SNS and LVH				
In Vitro Studies				
MicroRNAs	Study Model	Findings	miRNA Targets	Reference
↓ miR-143/145	Vascular smooth muscle cells (VSMCs) obtained from miR143/145-/- mice	miR-143/145 deficiency reduces the contractility of vascular smooth muscle cells.	ACE	[22]
↓ miR-483-3p	VSMCs—human and rat aortic smooth muscle cells	miR483-3p is reduced after in vitro stimulation with angiotensin II, which activates the renin angiotensin aldosterone system (RAAS).	Multiple components of the RAS: ACE1, ACE2, AGTR2	[21]
↑ miR-130a	VSMCs were prepared from the thoracic aorta of Sprague–Dawley rats	miR-130a induces the proliferation of VSMCs, by targeting GAX, which has inhibitory actions on VSMCs proliferation.	GAX	[24]
↑ miR-124, miR-135a	HeLa cells	Mineralocorticoid receptor NR3C2 is a target of miR-124 and miR-135a, which can be involved in the regulation of RAAS.	NR3C2	[39]
↑ miR-29b, miR-129, miR-132, miR-212	Cardiac fibroblasts and HEK293N cells	Overexpressed miRNAs activate Gαq/11, ERK-1/2 and AT1R.	AT1R	[29]
↑ miR-132, miR-212	H9c2 cells and primary cardiomyocytes	MiRNAs 132 and 212 were overexpressed regulating FoxO3 inducing LVH.	FoxO3	[40]
↑ miR-125b, miR-132, miR-146b ↓ miR-181b, miR-204, miR-300	Cardiac fibroblasts treated by AngII	A group of dysregulated miRNAs when treated with AngII, demonstrating important roles in hypertension and cardiac fibrosis.	MMP9, MMP16, TIMP3	[28]
↓ miR-155	Primary VSMCs from the aorta of C57/BL6 mice	Angiotensin II stimulation decreases expression of miR-155, inducing cell proliferation and survival.	AT1R	[23]
↑ miR-19a, miR-19b	Cardiomyocytes derived from neonatal rats stimulated with ET-1	MiR-19a and miR-19 promoted cardiomyocyte hypertrophy by regulating atrogin-1 and MURF-1.	Atrogin-1, MURF-1	[41]
↑ miR-27a	VSMCs stimulated with Ang-II	MiR-27a was overexpressed generating proliferation, migration and vascular dysfunction.	aSMA	[25]
↓ miR-133a	HUVECs stimulated with Ang-II	MiR-133a was downregulated, increasing PRR expression, which will exacerbate the signaling pathway of the RAAS, promoting apoptosis.	PRR	[27]
↑ miR-155	Cardiomyocytes stimulated with Ang-II	MiR-155 was overexpressed reducing IKBKE promoting inflammation and cardiomyocyte hypertrophy.	IKBKE	[42]

Table 1. Cont.

MicroRNAs in RAAS, SNS and LVH				
In Vitro Studies				
MicroRNAs	Study Model	Findings	miRNA Targets	Reference
↑ miR-19a, miR-21, miR-29b, miR-199b	Cardiac fibroblasts and ipsc-derived cardiomyocytes stimulated with ET-1	MiR-21 was overexpressed, leading to cardiac hypertrophy and fibrosis.	SPRY1	[43]
↑ miR-122	Rat aortic adventitial fibroblasts	MiR-122 was overexpressed, promoting reduced autophagic flux and increased cell migration, oxidative stress, inflammation and apoptosis.	SIRT-6, ELA, ACE2	[26]
In Vivo Studies				
↑ miR-135a, miR-376a	Spontaneous hypertensive rats	Downregulation of Agtrap transcript by miR-135a and miR-376a; disinhibition of AT1R signaling; miR-135a downregulates <i>Ptgr1</i> to increase the levels of LTB4, leading to the development of hypertension.	PTGR1, AGTRAP	[44]
↑ miR-107	Hypertensive mouse model	A polymorphism in the CHGA 3'-untranslated region known as C+87T (rs7610), promotes increased inhibition of CHGA by miR-107, leading to increased sympathetic nerve activity.	CHGA	[45]
↑ miR-21, miR-126, miR-146 ↓ miR-29b, miR-133a, miR-133b, miR-149, miR-150, miR-185	Cardiac hypertrophy C576BJ mice model	MicroRNAs were deregulated after aortic banding generating cardiac hypertrophy.	ANF, BNF, β-MHC	[46]
↑ miR-208a, miR-208b	Cardiac hyperaldosteronism (AS mice) and systemic hypertension (Ren)	Aldosterone and renin overexpression increases the expression of miR-208a and miR-208b inhibiting Sox6 and increasing cardiac hypertrophy.	Sox6	[47]
↑ miR-16, miR-21 ↓ miR-126	Spontaneous hypertensive rats	MiR-16 is overexpressed, reducing VEGF expression, promoting decreased angiogenesis and miR-21 is also highly expressed, attenuating Bcl2 expression, inducing apoptosis. miR-126 is downregulated increasing PI3KR2 expression by inhibiting the VEGFR pathway.	VEGF, Bcl2, PI3KR2	[32]
↑ miR-132, miR-212	Transaortic constriction mice (TAC)	MiRNAs 132 and 212 were overexpressed regulating FoxO3 inducing LVH.	FoxO3	[40]
↑ miR-132, miR-212	Angiotensin II-induced hypertensive rats	MiR-132/212 are increased in heart, kidney, aorta and plasma of angiotensin II-induced hypertensive rats.	PTEN, ERK/MAPK	[30]

Table 1. Cont.

MicroRNAs in RAAS, SNS and LVH				
In Vitro Studies				
MicroRNAs	Study Model	Findings	miRNA Targets	Reference
↑ miR-410, miR-495	Ang-II stimulated rat model promoting cardiac hypertrophy	MiR-410 and miR-495 are increased in this cardiac hypertrophy model.	Nppa, Nppb	[48]
↓ miR-181a	Genetically hypertensive mice (BPH/2J)	miR-181a was downregulated by increasing REN expression, increasing sympathetic nervous system activity.	REN1	[49]
↓ miR-34b	Spontaneous hypertensive rats	miR-34b was found downregulated in spontaneous hypertensive rats, increasing the levels of CDK6, leading to increased proliferation of VSMCs.	CDK6	[50]
↑ miR-22	Spontaneous hypertensives rats	miR-22 associated with dysregulation of Chga in brainstem cardiovascular control nuclei contributing to the pathogenesis of hypertension in SHR.	Chga	[51]
↑ miR-153	Spontaneous hypertensives rats	miR-153 upregulation leads to reduced Kv7.4 channel expression, vasoconstriction, and vascular wall thickening.	KCNQ4, Kv7.4	[52]
↑ miR-487b	Rat model of angiotensin II-induced hypertension	MiR-487b is upregulated by AngII and targets the vasoactive molecule IRS1, causing loss of adventitial and medial integrity.	IRS1	[53]
↓ miR-29b	Mouse model of Ang II-induced hypertension	MiR-29b is downregulated in mouse model of Ang-II-induced hypertension, promoting LVH.	COL-I, TGFb	[54]
↓ miR-19a, miR-19b	Ang-II-induced cardiac hypertrophy mouse model	Ang-II-induced pressure overload in rats reduced the expression of miR-19a and miR-19b, increasing the expression of PDE5A, generating LVH.	PDE5A	[55]
↑ miR-21	ALDO/SALT Hypertensives Mice	This study showed that miR-21 is upregulated by excess ALDO in the LV.	Spry1, Spry2, PTEN, PDCD4, Bcl2	[56]
Clinical Studies				
↑ miR-92a	Hypertensive patients (n = 240)	Plasma levels of miR-92a are increased in hypertensive patients and correlate with 24 h mean systolic and diastolic blood pressure, 24 h mean pulse pressure, 24 h daytime and nighttime pulse pressure, increased carotid intima-media thickness and carotid-femoral pulse wave velocity.	KLF2, KLF4, eNOS	[57]

Table 1. Cont.

MicroRNAs in RAAS, SNS and LVH				
In Vitro Studies				
MicroRNAs	Study Model	Findings	miRNA Targets	Reference
↑ miR-1, miR-208b, miR-499, miR-21 ↓ miR-133a, miR-26b	Hypertensive patients (n = 132)	Analysis of expression in PBMCs: miR-1, miR-133a, miR-26b, miR-208b, miR-499, and miR-21 show distinct expression profiles in hypertensive patients compared to healthy subjects; association with LVH.	MEF2a, BMPR2, PDCD4, PTEN	[58]
↑ miR-505	Hypertensive patients (n = 192)	Plasma levels of miR-505 are increased in hypertensive patients compared to healthy subjects and is positively correlated with systolic blood pressure; impaired endothelial migration and tube formation in culture by direct regulation of FGF18 and indirect regulation of HMGB1.	FGF18	[59]
↓ miR-133a	Hypertensive patients (n = 90)	Increased renal sympathetic nervous system induces downregulation of miR-133a.	PRR	[60]
↑ miR-202	Hypertensive patients (n = 182)	miR-202-3p exerts a protective role against EH by antagonizing the induction of sST2 by Ang-II.	ST2	[35]
↑ miR-29a, miR-29b, miR-29c	Hypertensive patients (n = 84)	Plasma levels of mir-29a, b and c were increased in patients with hypertension, with positive correlations with office systolic and diastolic blood pressure, office pulse pressure, 24 h mean systolic and diastolic blood pressure, 24 h mean pulse pressure and left ventricular hypertrophy.	COL1A1, COL1A2, COL3A1, VEGFA, TGF-β	[61]
↓ miR-136	Hypertensive patients (n = 110)	miR-136 is downregulated in patients with hypertension and is associated with elevated levels of RAAS biochemical markers.	Wnt, Notch3	[34]
↑ miR-516b, miR-600, miR-605, miR-623, let-7e ↓ miR-18b, miR-30d, miR-296-5p, miR-324-3p, miR-486-5p, miR-518b, miR-1236, miR-1227	Hypertensive patients (n = 194)	Plasma levels of miRNAs were distinct plasma miRNA expression pattern in hypertensive patients, compared with healthy subjects.	MAPK10, RICTOR, NFAT5, MAP3K9, MAP3K1, STAT3	[62]
↑ miR-132, miR-212	Hypertensive patients (n = 64)	miR-132/212 are increased in the arteries of hypertensive patients.	PTEN, ERK/MAPK	[30]
↓ miR-126	Hypertensive patients (n = 89)	Hypertensive patients showed significantly lower miR-126 expression levels in PBMCs, and positive correlation with 24 h mean pulse pressure.	SPRED-1, VEGF, PI3KR2	[63]

Table 1. Cont.

MicroRNAs in RAAS, SNS and LVH				
In Vitro Studies				
MicroRNAs	Study Model	Findings	miRNA Targets	Reference
↓ miR-155	Hypertensive patients (n = 64)	AT1R protein expression was positively correlated with systolic and diastolic blood pressure and negatively correlated with miR-155 expression level in PBMCs.	AT1R	[38]
↑ miR-21, miR-126, miR-196a, miR-451 ↓ miR-181a, miR-638, miR-663	Hypertensive patients (n = 14)	MiR-663 can regulate REN and APOE mRNA levels, whereas miR-181a regulated REN and AIFM1 mRNA.	REN, APOE, AIFM1	[36]
↑ miR-29, miR-30a ↓ miR-133	Hypertensive patients	MiRNAs are dysregulated in the plasma of hypertensive patients, associated with cardiomyocyte hypertrophy.	TGF-β1, Sp-1	[64]
↓ miR-25	Hypertensive heart disease patients	miR-25 is downregulated in the serum of hypertensive patients, elevating the renin expression, promoting RAAS activation.	REN	[37]
↑ miR-155	Hypertensive patients	MiR-155 is overexpressed and associated with inflammatory markers.	TGF-β1	[65]

Thus, the RAAS signaling pathway is modulated by miRNAs to regulate blood pressure, however, many other miRNAs can regulate these same RAAS genes in SAH, but further studies are needed to confirm this hypothesis.

### 3. MiRNAs and Sympathetic Nervous System Activation in SAH

The sympathetic nervous system (SNS) plays a fundamental role in blood pressure control through regulatory mechanisms expressed based on the release of neurotransmitters (epinephrine, norepinephrine and dopamine) that act on vessels, kidneys and heart. Thus, changes in the functions of this system are related to the development of cardiovascular disorders [66].

Cardiac output and systemic vascular resistance are the main target components for the action of sympathetic neurotransmitters through their release, by central and reflex mechanisms, and binding to their adrenergic ( $\alpha$  and  $\beta$ ) and dopaminergic receptors. These mechanisms, when activated, promote an arteriolar vasoconstriction (through  $\alpha$ -receptors) and an increase in cardiac output (through  $\beta$ -receptors) resulting in an elevation of blood pressure [67,68].

Activation of the SNS occurs in states of physical or emotional stress. However, in early stages of SAH, known as a hyperkinetic circulatory state, there is an increase in adrenergic impulse and a decrease in parasympathetic function [67], that is, there is an increase in plasma levels of sympathetic neurotransmitters concomitant with a loss of vagal inhibitory function. Furthermore, the magnitude of sympathetic activation parallels the severity of blood pressure elevation [68].

MiRNAs also participate in the regulation of the SNS. Specifically, miR-181a was downregulated in a genetic model of massive SNS activation, leading to increased renin expression, RAAS activation, and consequently hypertension in mice [49]. Overexpression of miR-135a and miR-376 were also associated with increased sympathetic nerve activity, contributing to exacerbated blood pressure and inflammation in spontaneously hypertensive rats [44].



In this context, miR-22 is also highly expressed in spontaneously hypertensive rats, reducing the expression of the Chromogranin A (CHGA), inducing greater central and peripheral nerve activity, contributing to the elevation of blood pressure [51]. A polymorphism in the CHGA 3'-untranslated region known as C+87T (rs7610), promotes increased inhibition of CHGA by miR-107, leading to increased sympathetic nerve activity, autonomic dysregulation, increased blood pressure and renal disease in a hypertensive mouse model [45].

Renal disease in hypertensive patients is very common due to increased renal sympathetic nervous system and this hyperactivation induces reduced expression of miR-133a [60]. This same study showed that the renal sympathetic denervation in these patients promotes increased expression of miR-133a, attenuating blood pressure, including being associated with decreased risk of developing hypertensive heart disease [60].

Other miRNAs, such as miR-200a, miR-200b, miR-205, miR-141, miR-192 and miR-429, are overexpressed in hypertensive patients with renal disease leading to nephrosclerosis, and the degree of elevation of these miRNAs was correlated with disease severity [69].

Furthermore, other miRNAs can be dysregulated due to activation of the sympathetic nervous system and inhibition of the parasympathetic nervous system in SAH, favoring the hemodynamic overload that generates long-term left ventricular hypertrophy.

#### 4. MiRNAs and Left Ventricular Hypertrophy in SAH

Under physiological conditions, stroke volume is regulated by preload through mechanisms that involve the extension of cardiac fibers at the end of diastole associated with resistance imposed by afterload [70]. Mechanical stress on the heart induces changes involving strain (related to increased afterload) and shear stress (related to blood friction against the vessel wall) resulting in compensatory adaptive effects when chronically altered in order to keep the cardiac output [71].

This mechanical stress is one of the triggering factors of cardiac remodeling, which occurs through processes of cardiomyocyte hypertrophy, hyperplasia, hypertrophy of non-muscle cells and interstitial proliferation [72]. Cardiac cell remodeling and hypertrophy, in response to mechanical stress in SAH, are the mechanisms that lead to left ventricular hypertrophy (LVH) [73]. LVH in SAH induces an increase in muscle mass and myofibril growth in parallel, generating concentric hypertrophy, reducing the internal area of the cardiac chamber. Hyperplasia of vascular structures and collagen accumulation also occur, favoring cardiac fibrosis [74].

Several miRNAs participate in the LVH process. In human-induced pluripotent stem-cell-derived cardiomyocytes stimulated with endothelin-1 (ET-1), miR-19a, miR-21, miR-29b and miR-199 are overexpressed, generating cardiac hypertrophy *in vitro*, however, when the analysis was performed on circulating miRNAs in the serum of chagasic patients with LVH, only miR-19a, miR-21 and miR-29b were overexpressed [43]. In cardiomyocytes derived from neonatal rats stimulated with ET-1, miR-19a and miR-19b promoted hypertrophy of these cardiomyocytes, reducing the expression of anti-hypertrophic target genes atrogin-1 and muscle RING-finger protein-1 (MURF-1), and it also activated the pro-hypertrophic pathway calcineurin/nuclear factor of activated T-cells (NFAT) [41].

On the other hand, Ang-II-induced pressure overload in rats reduced the expression of miR-19a and miR-19b, increasing the expression of phosphodiesterase 5A (PDE5A), generating LVH, including, as the authors show in the same study, that a model of transgenic mouse overexpressing miR-19a and miR-19b reduced PDE5A expression, decreasing cardiac hypertrophy [55], demonstrating that an expression pattern response of miRNAs in cell culture can be quite different from the response in animal models.

MiR-21, miR-126 and miR-146 are overexpressed in a C576BJ mouse model of cardiac hypertrophy, while miR-29b, miR-133a, miR-133b, miR-149, miR-150 and miR-185 were downregulated after aortic binding constriction [46]. MiR-132 and miR-212 are also overexpressed, decreasing the expression of the FoxO3 transcription factor, inducing attenuation of autophagy and activation of the pro-hypertrophic calcineurin/NFAT signaling pathway,

generating LVH, in both, in the culture of primary cardiomyocytes with different hypertrophic stimuli and in mice with transaortic constriction (TAC) and cardiac hypertrophy [40]. Likewise, in both in vitro and in vivo models stimulated with Ang-II, the expression of miR-410 and miR-495 is increased, modulating the expression of the hypertrophic genes *Nppa* and *Nppb*, promoting a robust hypertrophy of cardiomyocytes [48].

In an model of hypertensive mice overexpressing renin, it promoted SAH by increasing the expression of miR-208a and 208b, decreasing the expression of the transcription factor SOX-6, which is a repressor of alpha-myosin heavy chain (MyHC), increasing the expression of the latter gene, inducing LVH [47].

MiR-208b was also overexpressed in peripheral blood mononuclear cells from patients with SAH, in addition, other miRNAs were also overexpressed in these samples, such as miR-1, miR-21 and miR-499, while miR-26b and miR-133a were with reduced expression and this expression pattern correlated with LVH in these patients [58]. In studies in humans, animals and cells, the reduction of miR-133a expression promotes LVH or cardiomyocytes hypertrophy and the overexpression of this miRNA induces an anti-hypertrophic effect [75,76].

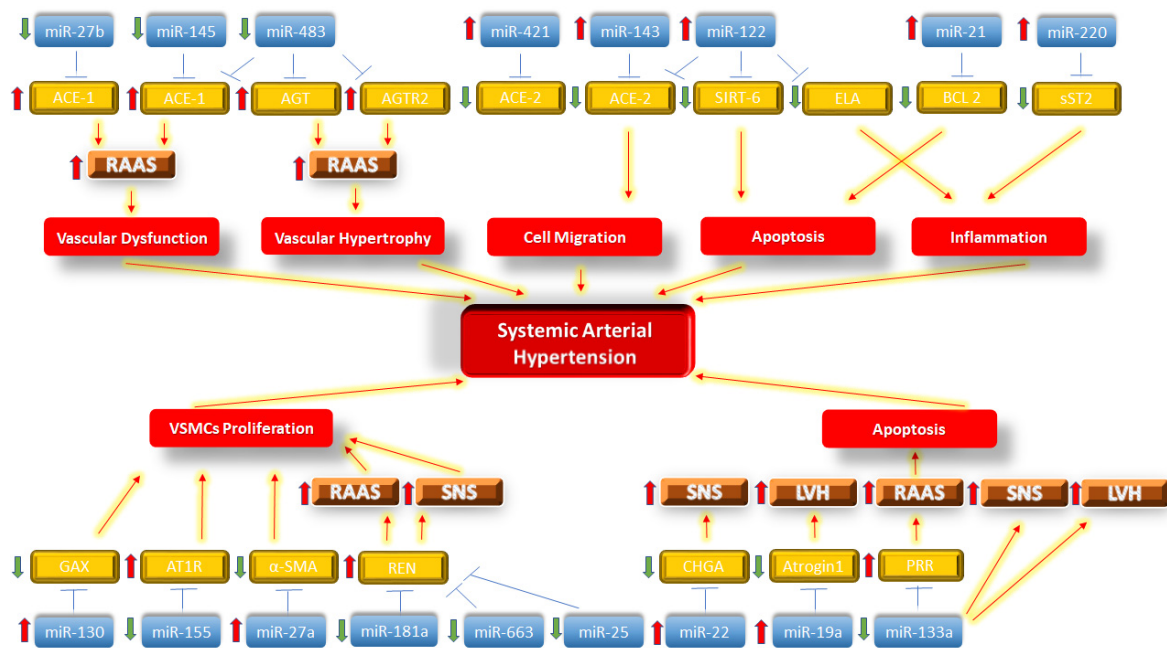
The miR-29 family (miR-29a, miR-29b and miR-29c), in turn, is overexpressed in the plasma of patients with SAH, regulating genes of the fibrotic and hypertrophic process, having a strong correlation with high blood pressure and LVH [61]. In agreement with these results, miR-29a was also shown with increased expression in the plasma of hypertensive patients with positive association with LVH [77].

On the other hand, miR-29b had its expression reduced in a mouse model of Ang-II-induced hypertension, increasing the expression of collagen-1 (COL-I), transforming growth factor- $\beta$  (TGF- $\beta$ ),  $\alpha$ -SMA, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), with reduced expression of the mothers against decapentaplegic homolog 7 (SMAD7) gene, inducing LVH. However, the induction of SMAD7 overexpression prevented the loss of miR-29b, decreasing the expression of COL-I, TGF- $\beta$ ,  $\alpha$ -SMA, TNF- $\alpha$ , IL-1 $\beta$ , reducing the inflammatory and fibrotic profile, in addition to attenuating the heart damage and LVH in these animals [54]. This finding demonstrates that the expression pattern of miRNAs may be different in hypertensive patients compared to animal models.

Another miRNA that is associated with the process of inflammation and cardiac hypertrophy is miR-155. In both in vivo and in vitro models of Ang-II-induced cardiac hypertrophy, miR-155 is overexpressed, reducing the expression of the inhibitor of nuclear factor kappa-B kinase subunit epsilon (IKBKE), promoting activation of the nuclear factor kappa-B (NF- $\kappa$ B), inflammation and cardiac hypertrophy [42]. In this same work, it was shown that the overexpression of the long non-coding RNA known as cytoskeleton regulator RNA (CYTOR), can serve as a sponge for miR-155, reducing the expression of this miRNA, and consecutively increasing the expression of IKBKE, inhibiting the NF- $\kappa$ B pathway, reducing inflammation and cardiomyocyte hypertrophy [42].

MiR-155 also had increased expression in the plasma of hypertensive patients, and this high expression was associated with inflammatory markers such as interleukin-6 (IL-6) and c-reactive protein [65]. Other circulating miRNAs also dysregulated in the plasma of hypertensive patients, such as miR-29 and 30a, are overexpressed, whereas miR-133 is downregulated [64], and these miRNAs are associated with the processes of inflammation and LVH [75,78].

Many other miRNAs are regulating genes and signaling pathways in SAH, including other non-coding RNAs; the main miRNAs that regulate signaling pathways in the RAAS, SNS and LVH are shown in a schematic representation in (Figure 1). Furthermore, other epigenetic processes, such as DNA methylation, histone acetylation and deacetylation, are also being modulated by changing transcriptomics during the pressure overload process promoting SAH.



**Figure 1.** Schematic representation of miRNAs regulating genes and signaling pathways in RAAS, SNS and LVH in SAH. Thick red upward arrow: upregulation of miRNA or target gene; thick green downward arrow: downregulation of miRNA or target gene; blue thin arrow: indicates that miRNA regulates that gene; red thin arrow: indicates that the change in the signaling pathway promotes a specific outcome.

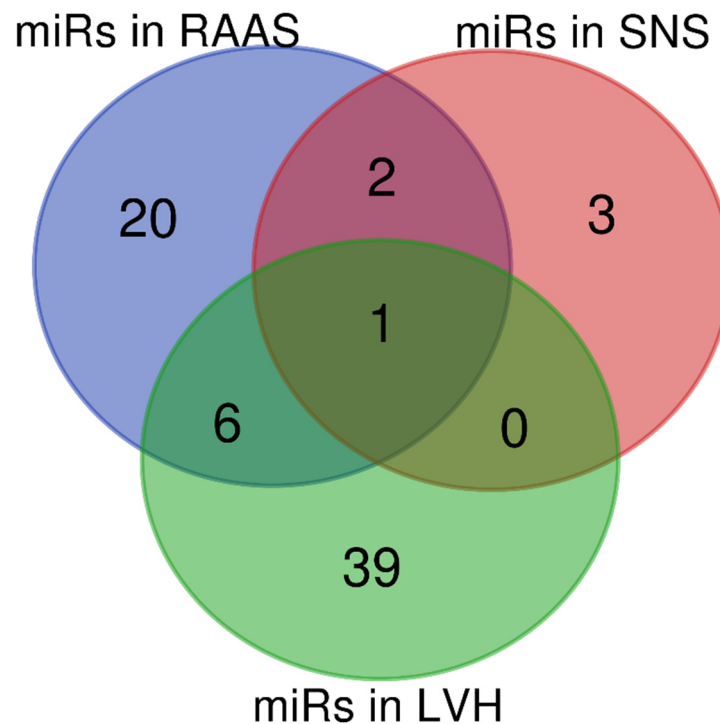
### 5. Overlapping miRNAs in RAAS, SNS and LVH in SAH

After reviewing the expression of miRNAs in RAAS, SNS and LVH in *in vitro*, *in vivo* and clinical studies, despite different methodologies applied in these works, it was possible to identify six miRNAs (miR-21 miR-155 miR-132 miR-29b miR-126 miR-212) with altered expression regulating RAAS and LVH processes. It was also possible to identify two miRNAs (miR-181a miR-135a) modulating the RAAS and SNS processes. No miRNA was identified associated with the SNS and LVH processes. However, one miRNA was observed to regulate all processes, the miR-133a (Figure 2).

MiR-133a plays an important role in cardiac development and is known to regulate some cardiovascular diseases [79–81]. Here it was identified that miR-133a is involved in the regulation of three processes that are fundamental for the development of SAH and the clinical worsening of the disease. In this context, miR-133a is downregulated regulating signaling pathways in RAAS, SNS and LVH, as previously described. Interestingly, it was identified that miR-133a is regulating the PRR gene, activating the RAAS and SNS, promoting LVH, aggravating the disease. In addition, miR-133a is associated with other signaling pathways such as  $\beta$ -MHC and atrial natriuretic factor (ANF).

In addition to regulating these three overlapping processes, miR-133a also regulates vascular remodeling and fibrosis through the membrane type-1 matrix metalloproteinase (MT-1 MMP) target gene. MiR-133a was also reduced in aortic fibroblasts exposed to biaxial cyclic stretch, generating tension and vascular remodeling, including being downregulated in thoracic aortic tissue of Ang-II-induced hypertensive mice and in spontaneously hypertensive mice [82].

In situations of myocardial ischemia that occur in many hypertensive patients, miR-133a is also downregulated, promoting an increase in MT-1 MMP, in addition to elevating other pro-fibrotic genes such as transforming growth factor beta receptor 1 (TGFBR1), latent transforming growth factor binding protein 1 (LTBP1), matrix metalloproteinase 9 (MMP9), phosphorylated Smad2 (pSMAD2) and COL1A1, inducing activation of TGF- $\beta$  signaling pathway, leading to vascular and cardiac fibrosis [83].



**Figure 2.** MiRNAs regulating RAAS, SNS and LVH.

Furthermore, miR-133a was shown to be reduced in the left ventricle of rats with chronic administration of AngII, increasing the expression of the COL1A1 gene, generating myocardial fibrosis [84]. All this evidence demonstrates that miR-133a plays a critical role in SAH, acting as a key element in this disease.

## 6. Conclusions

Several miRNAs are regulating target genes and altering signaling pathways in RAAS, SNS and LVH in SAH. Some of these miRNAs are associated and interact to activate these systems simultaneously and worsen the clinical status of these patients. Specifically, miR-133a has a key multiregulatory role in the three analyzed processes, regulating the PRR signaling pathway, and is also associated with other deleterious situations in SAH, such as cardiac fibrosis and myocardial ischemia. Thus, further studies are needed to analyze the expression of miRNAs in RAAS, SNS and LVH, and especially the activation of miR-133a as a potential therapy for inactivation of RAAS and SNS, inducing possible LVH attenuation in SAH.

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