Reduced Pulsatility Induces Periarteritis in Kidney: Role of the Local Renin–Angiotensin System

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Objective: The need for pulsatility in the circulation during long-term mechanical support has been a subject of debate. We compared histologic changes in calf renal arteries subjected to various degrees of pulsatile circulation in vivo. We addressed the hypothesis that the local renin–angiotensin system may be implicated in these histologic changes.

Methods and Results: Sixteen calves were implanted with devices giving differing degrees of pulsatile circulation: 6 had a continuous flow left ventricular assist device (LVAD); 6 had a continuous flow right ventricular assist device (RVAD); and 4 had a pulsatile total artificial heart (TAH). Six other calves were histologic and immunohistochemical controls. In the LVAD group, the pulsatility index was significantly lower (0.28 ± 0.07 LVAD vs 0.56 ± 0.08 RVAD, vs 0.53 ± 0.10 TAH; $P <$ 0.01), and we observed severe periarteritis in all cases in the LVAD group. The number of angiotensin II type 1 receptor–positive cells and angiotensin converting enzyme–positive cells in periarterial areas was significantly higher in the LVAD group (angiotensin II type 1 receptor: 350 ± 139 LVAD vs 8 ± 6 RVAD, vs 3 ± 2 TAH, vs 3 ± 2 control; $P < .001$; angiotensin-converting enzyme: 325 ± 59 LVAD vs 6 ± 4 RVAD, vs 6 ± 5 TAH, vs 3 ± 1 control; $P < .001$).

Conclusions: The reduced pulsatility produced by a continuous flow LVAD implantation induced severe periarteritis in the kidneys. The local renin–angiotensin system was up-regulated in the inflammatory cells only in the continuous flow LVAD group.

CSP

The necessity of maintaining pulsatility in the systemic circulation during long-term mechanical support has been a subject of debate. Recently, simpler and smaller continuous flow blood pumps have become more prevalent. The diminished pulsatility created by support from a continuous flow left ventricular assist device (LVAD) is physiologically abnormal, and some changes to the structure of the aortic wall and the renal artery have been reported.[1,2] Continuous flow LVAD support has been reported to cause renal cortical artery hypertrophy and inflammatory cell infiltration in the renal cortex.[2] However, the mechanisms leading to those morphologic changes are still unclear.

In this study, we examined the renal arteries of calves implanted with several different types of circulatory support devices delivering various degrees of systemic arterial pulsatility. We observed severe inflammatory and morphologic changes in the kidney only in those calves with continuous flow LVADs. In addition to its pressor effect, angiotensin II (Ang II), the physiologically active component of the renin–angiotensin system (RAS), has a variety of nonhemodynamic actions, including cell growth, as well as proinflammatory and profibrogenic actions through the Ang II type 1 receptors (AT1R).[3] Many of these actions are associated with cardiovascular and renal disease.[4] Many tissues are thought to be capable of local Ang II production via the tissue-specific local RAS.[5-9] This locally produced Ang II acts on tissue through resident Ang II receptors. We directed our attention to the local RAS as

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
Ang II = angiotensin II
AT1R = angiotensin II type 1 receptor
eNOS = endothelial nitric oxide synthase
LVAD = left ventricular assist device
pa = periarterial areas
RAS = renin–angiotensin system
RVAD = right ventricular assist device
TAH = total artificial heart

a possible mechanism for those pathologic changes, and we demonstrated by immunohistochemical analysis that AT1R and angiotensin-converting enzyme (ACE) were found in inflammatory cells that had infiltrated the kidneys of calves with continuous flow LVADs.

Methods

Animals and Device Description

Twenty-two male Holstein calves (99.8 ± 16.7 kg) were used in this study. A continuous flow LVAD was implanted in 6 calves, creating the condition of reduced systemic arterial pulsatile perfusion; a continuous flow right ventricular assist device (RVAD) was implanted in 6 calves, representing the condition of pulsatile perfusion and as a biomaterial control. The RVAD did produce reduced pulsatility in the pulmonary circulation; however, pulsatility was maintained in the systemic circulation. A pulsatile total artificial heart (TAH) was implanted in 4 calves to study pulsatile perfusion. Six normal calves were used as normal histologic and immunohistochemical controls. As shown in Table 1, the devices were implanted for various durations ranging from 22 to 95 days.

TABLE 1. Characteristics of calves with mechanical support devices and normal control calves

	No.	Implant duration (d)	Body weight (kg)
LVAD (n = 6)	1	39	84.0
	2	29	93.0
	3	31	83.0
	4	31	86.0
	5	30	92.0
	6	95	83.0
	Avg.	42.5 ± 26.0	86.8 ± 4.5
RVAD (n = 6)	1	30	93.0
	2	29	96.0
	3	25	160.0
	4	22	95.6
	5	30	96.9
	6	30	113.2
	Avg.	27.7 ± 3.4	109.1 ± 26.0
TAH (n = 4)	1	83	105.0
	2	28	113.0
	3	92	110.5
	4	67	110.0
	Avg.	67.5 ± 28.3	109.6 ± 3.4
Control (n = 6)	1	—	100.0
	2	—	90.0
	3	—	90.0
	4	—	110.5
	5	—	90.0
	6	—	101.0
	Avg.	—	96.9 ± 8.4

LVAD, Left ventricular assist device; *RVAD,* right ventricular assist device; *TAH,* total artificial heart.

Animal Care

This study was approved by the Cleveland Clinic's Institutional Animal Care and Use Committee, and all animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996.

Implant Procedure

On arrival at the facility, all calves were quarantined for at least 14 days in the Biological Resources Unit. The calves were fasted for 12 hours before surgery. Anesthesia was induced with ketamine, 10 mg/kg intramuscularly, and isoflurane via mask inhalation. Each animal was then intubated, and anesthesia was maintained with isoflurane (1.0%–2.0%) and oxygen.

LVAD Implantation

The CorAide continuous flow left ventricular assist system (Arrow International, Reading, Pa), originally developed at the Cleveland Clinic, is a centrifugal continuous flow pump.[10] Through a left thoracotomy, the outflow graft of the pump was anastomosed to the descending aorta, and the inflow cannula of the pump was inserted into the left ventricle. An ultrasonic perivascular flow probe (Transonic Systems Inc, Ithaca, NY) was placed around the outflow graft for continuous monitoring of the pump output. Arterial pressure was measured in the carotid artery by a fluid-filled pressure-monitoring line. After surgery, intravenous nitroprusside was administered to maintain mean arterial pressure at less than 125 mm Hg and pump flows at greater than 3.5 L/min.

RVAD Implantation

The Cleveland Clinic's DexAide blood pump is a centrifugal, continuous flow blood pump, constructed of the same materials as the CorAide left ventricular assist system,[11] but with a modified design. Through a left thoracotomy, the outflow graft of the pump was anastomosed to the pulmonary artery, and the inflow cannula of the pump was inserted into the right ventricle under cardiopulmonary bypass support. An ultrasonic perivascular flow probe was placed around the outflow graft. Systemic arterial pressure was measured in the carotid artery by a fluid-filled pressure-monitoring line. After cardiopulmonary bypass was discontinued, the RVAD was initiated.

TAH Implantation

The Cleveland Clinic's MagScrew TAH is an implantable pulsatile TAH system.[12] A right fourth intercostal thoracotomy was performed. Under cardiopulmonary bypass support, the native ventricles