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Outline the pathophysiological basis for the use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in congestive cardiac failure.

Cardiac failure causes decreased cardiac output, leading to decreased arterial pressure. This causes baroreceptor activation and inappropriate activation of the renin-angiotensin-aldosterone system.

Physiology of RAAS

- Renin is released by the juxtaglomerular cells in the kidney, in response to :
  - Decreased afferent arteriolar pressure
  - Decreased delivery of NaCl to the distal tubule
  - Sympathetic stimulation
- Renin cleaves angiotensinogen to angiotensin I
- Angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE), which is found in the lung vascular endothelium:
  - Small amount of ACE-independent conversion occurs in the plasma
- ACE also has effects on degradation of bradykinin
- Angiotensin II effects:
  - Altered peripheral resistance:
    - Direct vasoconstriction (activation of AT_1 receptors) → leading to LVH
    - Stimulates norad release from sympathetic nerve terminals
    - Stimulates ADH secretion
  - Renal effects:
    - Efferent arteriolar constriction
    - Increased tubular Na^+ reabsorption
    - Aldosterone release → increased Na^+ reabsorption
    - Overall effect is to increase blood volume and blood pressure
  - Altered cardiovascular structure:
    - Increased production of growth factors and extracellular matrix
    - Vascular hyperplasia and stimulation of cardiac fibroblasts
    - Net effect is pathological alterations involving cardiac hypertrophy and remodelling → increased morbidity/mortality
- Bradykinin causes vasodilation, and is thought to oppose vascular remodelling by ATII
- End results of RAAS activation are:
  - Excessive salt and water retention
  - Increased afterload
  - Inappropriate ventricular remodelling

Effects of ACEI

- Prevent conversion of angiotensin I to angiotensin II
- ACEI cause:
  - Effects of ATII inhibition:
    - Decreased afterload and decreased systolic wall stress
    - Improved cardiac output and stroke volume
    - Improved arterial compliance
    - Decreased systemic blood pressure
    - Decreased renovascular resistance → increased renal blood flow → natriuresis
    - Decreased aldosterone secretion (although aldosterone secretion is stimulated by other factors)
    - Decreased Na^+ and water retention
    - Prevention of degradation of bradykinin → vasodilation and opposition of vascular remodelling
    - Reduced ventricular dilatation; restoration of heart to normal elliptical shape
  - Potentiation of effects of diuretics
- Small amounts of ATII are always present, as ACE inhibition is never complete

Effects of ARBs

- Bind to AT_1 receptor > AT_2 receptor and cause blockade
- Blocks most effects of ATII:
  - Decreased contraction of vascular smooth muscle; decreased sympathetic stimulation
  - Decreased vasopressin release; decreased aldosterone secretion
  - Decreased renal effects
  - Decreased cellular hypertrophy and hyperplasia
- Although ARB binding to AT_1 receptors is competitive, the inhibition of biological responses to ATII by ARBs is often insurmountable

Comparison between ACEI and ARBs

- ARBs reduce activation of AT_1 receptors more completely than ACEI, as ATII can still be generated by non-ACE pathways
- ARBs allow activation of AT_2 receptors
- ACEI increase levels of bradykinin