Why Synthetic Vasopressin and Oxytocin Analogs Should be Considered in the Treatment of Cardiogenic Shock: A Personal Perspective

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Abstract
Cardiac instability can be brought about by a number of hemodynamic dysfunctions such as deficits in myocardial ventricular or atrial contractility, Myocardial Infarction (MI), electrical-conduction disturbances, myocardial valvular problems, structural changes in the pericardium, coronary arterial flow problems or combinations of these factors. Cardiogenic Shock (CS) is characteristically defined as a cardiac disorder which results in clinical, biochemical and molecular cell manifestations in inadequate tissue and cellular perfusion. Clinically, the patient presents with persistent hypotension which is unresponsive to volume replacement in conjunction with end-organ hypoperfusion requiring intervention with pharmacological/mechanical support. The end result of this hypoperfusion is a deficit in coronary microcirculatory blood flow and nutrition to the tissues and cells of the ventricles and atria.

Introduction
Prior to the utilization of early revascularization, CS had an in-hospital mortality approaching/exceeding 80%. Patients with Killip class IV characteristics have been reported to exhibit mortality in excess of 80% [1]. Although early trials of mechanical support often appeared to be beneficial, such treatments did not always result in increased survival of the patient. Coupling early revascularization with Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Surgery (CABG) result in significant reductions in overall 6 and 12-month mortality. However, there have been limits requiring increased hospitalization often resulting in super-infections resulting in increased financial costs and subsequent deaths.

The major problem in CS is a profound depression in myocardial contractility causing markedly reduced cardiac output, low arterial blood pressure, severe coronary microcirculatory ischemia, followed by further reductions in myocardial contractility leading to a vicious downward cycle resulting in deficits in capillary blood flows to critical organ regions (i.e., lungs, brain, liver and kidneys) leading to Multiple Organ Failure (MOF). Cardiogenic shock is a self-perpetuating syndrome as hypotension results in decreased coronary perfusion, thus exacerbating ischemia causing decreased stroke volume and augmenting oxygen demand. Whatever the initiating circumstance causing CS, and whatever the effects these initiating circumstances may have on circulating blood volume and cardiac output, the overall vasomotor response results in a functional decrease in transcapillary exchange in the cardiac and peripheral organs-tissues [2-5]. This is the all-important trigger mechanism that sets in motion the chain of events which, if not promptly corrected, will generate the refractory and ultimately irreversible characteristics of the CS syndrome. The strategic role of microcirculatory failure in CS is further supported by voluminous experimental and clinical studies that appear to demonstrate that any therapy which directly or indirectly improves local coronary microcirculatory-tissue blood flows is beneficial [1-9]. But, most of these studies do not emphasize drugs or techniques that are either suitable or reliable for clinical use in a...
"tried-and-true-manner" in CS.

Problems with Use of Commonly-Used Vasopressors in Cardiogenic Shock

Many different drugs are commonly used to raise arterial blood pressure in CS; these being referred to as "vasopressors". Although the idea to utilize these agents to raise arterial blood pressure is, at first glance, a reasonable hemodynamic basis for their use, they are often discarded because while they often raise blood pressure, they do not effectively increase tissue perfusion either in the myocardium or periphery [1,3-9]. The net effects of these vasopressors on the Pressure-Resistance relationships (P-R) which determine blood flows in the peripheral tissues are often incompatible with either increased blood flow or increased survival of the patient. Despite these drawbacks, new vasopressors continually are searched-for. What physicians, surgeons and ER personnel often forget is that in "low-flow states" such as CS, local tissue blood flows are primarily conditioned by postarteriolar microcirculatory dynamics [2-4,7,10]. Effective drugs must be able to pharmacologically modify the postarteriolar muscular microvessels (i.e., metarterioles, precapillary sphincters, and venules) to sustain myocardial and peripheral effective capillary nutritive blood flows, distribution, and outflows (i.e, venous return) [6,7,9]. For more than 50 years, our laboratories have used this principle to design and implement the use of "selective vasopressor agents" [10-36]. We have done this by directing the synthesis of new drugs by changing the molecular structures of Vasopressin (VP) and Oxytocin (OT) [10-37].

Design and Use of New Peptides with Selective Vasoconstrictor and Vasodilator Actions

Until recent experimental and clinical studies, neither VP nor OT were given little serious thought as useful vasoactive drugs in the treatment of different forms of circulatory shock, including CS, particularly in view of either VP’s well-documented coronary and unselective peripheral constrictor actions or OT’s “iffy” cardiovascular actions [38,39]. VP has been demonstrated in numerous animal and human studies, to cause reductions in coronary arterial flows that become severe, resulting in ischemia [38-42]. However, some studies suggest that this may not happen or VP may induce vasodilatation (in pulmonary and cerebral vascular beds) [see 41-43, for reviews], despite evidence to the contrary [38-42]. We believe this controversy might be related to different actions on the major, surface coronary vessels versus the smaller arterioles deep within the walls of the ventricles. Another factor that has to be considered in all forms of Circulatory Shock (including CS), is a massive release of VP from the paraventricular and supraoptic nuclei of the hypothalamus which often will reach levels in the blood which are 20-200 times normal [42,43]. In addition, it has been demonstrated that cardiac muscle has the capacity to release VP [42,43]. Added to this is the number of studies which have shown that administration of VP often causes decreases in cardiac output and decreases in perfusion of the intestinal tract, pancreas, liver and kidneys [42-44]. These effects can and often lead to life-threatening situations. On a molar basis, VP is one of the most powerful peripheral vasoconstrictor agents, even more powerful than angiotensin II [41-44]. Most arteries and arterioles (including coronary vessels), in the body, show greater sensitivity to VP compared to angiotensin II, in terms of both affinity and intrinsic activity [20,23,34,36,37]. However, evidence has accumulated to suggest that some synthetic analogs of VP and OT may not promote coronary vasoconstrictor effects, and may actually produce coronary arterial relaxation of the vascular smooth muscle cells in intact human hearts, resulting in vasodilator actions [45-48] coupled to selective vasoconstrictor actions on microvessels in the periphery [10-36].

At least six synthetic analogs of VP, namely [2-phenylalanine, 8-lysine] vasopressin (PLV-2) ; [8-ornithine] Vasopressin (OV), [2-phenylalanine, 8-ornithine] vasopressin (POV) , [3-Ileu, 8-ornithine ] vasopressin (ILV), 1-deamino-[2-phenylalanine, 8-arginine] vasopressin (DAVP) and [2-phenylalanine, 3-isoleucine, 8-ornithine] vasopressin (PIOV) as well as at least four analogs of OT (i.e., [8-ornithine ] oxytocin; [8-arginine]oxytocin, [4-threonine] oxytocin, and 1-deamino-dicarba-oxytocin) have been found to exert significant vasodilator properties in the coronary circulation and exert ceilings on vasconstriction in the peripheral microcirculation along with selective actions on the muscular venules in the latter [12-37, 48; unpublished findings]. Our ongoing animal (i.e., rat, rabbit, dog, and sub-human primates) and human studies have determined the functional contributions to, and interactions with, the amino, phenolic, hydroxyl, and aromatic groups as well as basicity in positions 1,2,3 and 8, respectively, to or with hormone-receptor affinity and intrinsic (contractile/relaxant) activity. These goals have been achieved by analyzing the dose-response curves of VP and OT octapeptides lacking one or more of these functional groups. The findings, so far, demonstrate that: 1) the structure-action relationships for the peptide-induced responses (i.e., contractions/relaxations) on the microvessels and various blood vessels (including the coronaries and perfused hearts) vary with the particular micro- and macrovessel type (i.e., arteriole, precapillary sphincters, and venules) [12-36, 50, unpublished findings]; 2) the amino, phenolic, and aromatic groups in positions 1,2, and 3, respectively, are not only important for hormone-receptor affinity but intrinsic activity as well [17-20,23-28,33-35,37,48]; 3) the potency (EC 50) values for arginine-VP as well as the potencies and intrinsic activities of synthetic VP and OT analogs varied with the type of microvessel examined [17-20,23-28,33-35,37,48]; 4) many of the VP and OT analogs (e.g., PLV-2, DVAP, POV, PIOV, [8-ornithine]-oxytocin, [4-threonine]-oxytocin) produced various degrees of vasodilatation in intact and isolated coronary arteries, including in humans[14,34,36,37,48-53]; and 5) several of the modified octapeptides significantly improved permanent survival in animals subjected to CS and other forms of circulatory shock (i.e., hemorrhage, trauma, sepsis, and combined injuries) [11-15,19,24,32-34,37,48].

Beneficial Effects of VP Analogues in Different Types of Experimental Cardiogenic Shock

Using two different models of CS in rats and pigs with four different VP analogues (PLV-2, DVAP, POV, and PIOV), we have, so far, found increased survival and coronary blood flows approaching near normal levels. Interestingly, these four analogues (to different degrees) also vastly improved kidney and pulmonary blood flows as well as resulting in a decrease in release of several cytokines and chemokines into the blood stream. Although we have not, as yet, explored the possible beneficial effects of the OT analogues in these two different CS models in pigs or rats, we are hopeful that a number of the OT derivatives will provide beneficial effects.

Conclusion and Future Thoughts

Pharmacologic manipulation of the functional behavior of
organ systems is by no means a novel or impractical concept; it is a well-established objective in clinical pharmacology. Renal function, for example, can be manipulated with almost exquisite precision. Comparable, precise manipulation of the coronary microcirculation in cardiogenic shock has long been sought. It thus follows, that the design of new drugs which could manipulate the failing coronary microvasculature in CS would be of great and life-saving benefit. This reasonable approach has not achieved this goal, as up to now, drugs with selective vasoconstrictor/vasodilator actions were not available or tested in CS. In view of our ongoing studies, we believe effective and precise pharmacologic manipulation of the microcirculation in CS is very much alive and optimistic. It is, thus, our hope that such clinical trials using some of the peptide analogues discussed, herein, will get underway in the near future.

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References


