COMMENTARY

Renal-dose dopamine: will the message now get through?

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Deterioration in renal function is common in critically ill patients under intensive care.[1] It lengthens patients' stay in the intensive-care unit and their risk of death. Management of such cases is restricted to supportive measures, and it is easy to see why critical-care doctors are eager for any new approach that might prevent the onset of renal dysfunction or hasten its recovery.

Dopamine is widely used in intensive-care units as an inotropic and vasoactive agent. At low or "renal" doses (0·5–2·0 mg/kg per min) its actions are mainly dopaminergic but at higher doses unpredictable β and α adrenergic actions occur. Low doses result in plasma dopamine concentrations about 100 times higher than due to endogenous secretion but there is huge variation between individuals. Furthermore plasma-dopamine clearance is much lower in critically ill patients than in healthy people, and again there is considerable variation, so plasma concentrations are impossible to predict.[2]

In laboratory animals and healthy volunteers low doses of dopamine increase renal blood flow and glomerular-filtration rate and inhibit proximal-tubular reabsorption of sodium, which result in natriuresis.[3] Such findings have not been clearly shown in patients in intensive care. Indeed the very concept of selective renovascular low-dose dopamine infusion in the critically ill has been challenged on grounds of the different clearance characteristics of the drug.[2] Despite no evidence of benefit, low-dose dopamine has been widely embraced as an option for preventing renal failure in the critically ill. A wealth of reviews, commentaries, and editorials urging that the practice be stopped until efficacy is proved[1,3–9] have largely been ignored.[3–9]

However, not all commentators have been clear about the need for an evidence base before dopamine is used in this setting. When a small study of only seven healthy volunteers was reported to show that simultaneous administration of norepinephrine and low-dose dopamine preserves renal blood flow,[10] the accompanying commentary[11] stated that "despite the limitations . . .", by which the author presumably meant that the study was too small, uncontrolled, and irrelevant to the critically ill, ". . . the results are sufficiently strong to recommend the use of low dose dopamine in all patients with septic shock requiring norepinephrine, since the potential benefits of preserved renal perfusion should outweigh any risks".

Although it is surprising that the study published in today's *Lancet* was ever undertaken, given the clear directives from the critical-care and renal-medicine communities over the past decade, the results of this well-designed trial may at last have the desired effect on those who remain enthusiasts for renal-dose dopamine. This Australasian trial confirms that low doses of dopamine in critically ill patients with early renal dysfunction has no effect on serum creatinine or on requirements for renal-replacement therapy or on the duration of stay in the intensive-care unit. The mortality rate was similar in the dopamine and placebo groups.

Low-dose dopamine is thought to be harmless. That is not true. Dopamine can suppress respiratory drive, increase cardiac output and myocardial oxygen consumption, and trigger myocardial ischaemia and arrhythmias. The drug can also induce hypokalaemia and hypophosphataemia, both potentially dangerous in the critically ill, and it may predispose to gut ischaemia.[12] Dopamine disrupts metabolic and immunological homoeostasis through effects on a variety of hormones and T-cell function.[13] There are also concerns about adverse cardiac effects of dopamine in patients with ischaemic heart disease,[14] and there is a suggestion that dopamine is nephrotoxic in diabetic patients exposed to radiocontrast media.[15] Central venous cannulation itself is not without risk and extravasation of dopamine during the infusion can lead to ischaemia and gangrene.

The large study published this week amply confirms the lack of renal protection offered by low-dose dopamine in the critically ill. Dopamine can also be harmful. It is time to stop hedging: there is no justification for using "renal dose" dopamine in the critically ill.

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Rekindling old controversy on elusive lair of latent tuberculosis

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Understanding how *Mycobacterium tuberculosis* lies quiescent for years if not decades, how the immune system fails to detect and eradicate it, and the nature of the stimuli for its reactivation remains nearly as uncertain today as in Robert Koch's time. An even simpler issue, but no less elusive, has been the question of where tubercle bacilli reside during latency. At issue is whether latent bacilli inhabit old granulomatous lesions in the lung and lymphatics or whether they reside remotely in non-granulomatous tissue. In today's *Lancet* R Hernandez-Pando and colleagues rekindle this smouldering controversy with molecular evidence that normal-appearing human lung, rather than granulomatous lesions, may harbour latent *M tuberculosis*.

The healed pulmonary and tracheobronchial granulomas have always seemed intuitively appealing candidates as the home of latent organisms. These encapsulated, sometimes calcified, lesions might offer sanctuary from cellular immune surveillance as well as an anaerobic, acidic, and lipid-rich environment that might stimulate the bacteria to adopt a microbial form of hibernation. On the other hand, haematogenous spread occurs during primary infection, so metastatic implantation of bacilli in remote body sites could be at the root of latency.

In primary tuberculosis, bacteria multiply more or less unimpeded for several weeks both at the initial infection site in the distal alveolar spaces and in the regional lymphatics. As acquired immunity mounts, granulomas arise, contain the bacilli, and later heal in these same locations, leaving behind the classic Ghon complex—calcified granulomas at the lung bases and hilar nodes.[1] During early primary infection the bacilli may also migrate beyond the lymphatics, entering the pulmonary vascular circulation and possibly the systemic circulation. The fact that the well-known calcified Simon foci of the pulmonary apices have been found in children attests to early haematogenous spread during primary infection.[2] By virtue of lymphatic and haematogenous dispersal during early primary tuberculosis, tubercle bacilli may, in theory, establish persistence in virtually any cell in any organ.

The controversy as to the source of reactivation can be traced well into the early half of the 20th century. Of particular value are the numerous human necropsy studies of various pulmonary lesions for infectivity to guineapigs—animals exquisitely sensitive to tuberculosis. Griffith, for example, described 178 encapsulated human lesions that contained microscopic evidence of acid-fast bacilli but were sterile both microbiologically and by passage into guineapigs.[3] Similarly, Feldman and Baggenstoss succeeded in transmitting *M tuberculosis* to guineapigs with only one specimen from among 68 encapsulated pulmonary lesions from necropsies of patients who had died of causes other than tuberculosis.[4] These investigators concluded that encapsulated, granulomatous lesions in the human lung were sterile, and that patients with such lesions who later developed tuberculosis must have sustained either exogenous reinfection or endogenous reactivation from another body site. By contrast, Opie and Aronson identified high percentages of viable tubercle bacilli in human pulmonary granulomas: 33% from partly fibrotic lesions, 23% from caseous encapsulated lesions, 4% from caseous calcified lesions, and 20% from calcified nodular lesions from among 169 individuals.[5] Opie and Aronson entertained the hypothesis that viable bacilli might be passed to guineapigs from the associated tissues external to the granulomatous lesions rather than from the central core of the lesions. To address this possibility they prepared human tissue homogenates from unaffected portions of the lung from 33 necropsy specimens, and, surprisingly, 15 of these contained viable *M tuberculosis* infectious for guineapigs—a finding that strongly suggested that latent bacilli reside in apparently normal tissue.

The debate on the source of post-primary tuberculosis has continued to smoulder for more than a half century. Proponents of the granuloma have pointed out that physiological variants of the bacilli such as anaerobic forms or non-acid-fast L-forms might remain viable in vivo, but be poorly cultivable in vitro or during abrupt passage to animals.[6,7] Another argument in favour of the granuloma was the development of an in-vitro anaerobic model of latent *M tuberculosis* in which gradual oxygen withdrawal leads to a non-replicating but viable state.[8] Partly anaerobic conditions might be expected to prevail within the centre of caseous or calcified granulomatous lesions. Moreover, in this in-vitro state of latency, tubercle bacilli become susceptible to anaerobically active drugs such as nitroimidazoles[9,10] and express different antigens and metabolic pathways[11,12] from those prevailing when they are actively growing in the presence of oxygen. Veterinary tuberculosis experts, on the other hand, have not lost sight of early work showing infectious organisms in normal apical lung tissue and have reproduced Opie and Aronson's finding in animal models of tuberculosis.[13]

Hernandez-Pando and colleagues have revisited the 1927 work of Opie and Aronson, this time using PCR rather than guineapig passage. Employing both conventional solution PCR as well as in-situ PCR on small blocks of grossly normal-appearing lung tissues from 47 Ethiopian and Mexican patients who had died of causes other than tuberculosis, the investigators amplified DNA specific for *M tuberculosis*. 36% of these non-granulomatous specimens were positive for *M tuberculosis* DNA by conventional PCR and 32% by in- situ PCR; the concordance between the two methods was 79%. The in-situ PCR also turned up the surprising observation that in some instances mycobacterial DNA was present in cells other than macrophages, such as