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Official publication of the American College of Chest Physicians



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*Chest* 2001;120;275-282  
DOI 10.1378/chest.120.1.275

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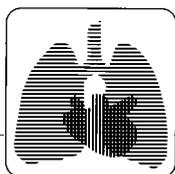
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A M E R I C A N C O L L E G E O F



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## opinions/hypotheses

# Is Amiodarone an Underrecognized Cause of Acute Respiratory Failure in the ICU?\*

Houman Ashrafian, and Patrick Davey, MD

Amiodarone is a commonly used anti-arrhythmic agent, with well-recognized chronic toxicity. Less well known is amiodarone's potential to cause acute lung damage, which can be severe or, occasionally, life-threatening. Lungs that have already been exposed to physical insults, such as the lungs of patients undergoing cardiac surgery, are particularly susceptible to acute pulmonary toxicity (APT). Unfortunately, cardiac surgery is one of the clinical scenarios in which amiodarone is most commonly used. After reviewing the data, and even in the context of difficulties and discrepancies in the existing literature, we contend that there is sufficient evidence of amiodarone's potentially serious side-effect profile in surgical ICU patients to advise continued caution in its use with this severely ill patient group. We suggest that amiodarone has a potentially important, though underrecognized, role in inducing an APT/ARDS in some patients, such as those undergoing cardiac surgery. We also provide a hypothesis to explain the mechanism by which amiodarone causes lung damage. (CHEST 2001; 120:275-282)

**Key words:** adult respiratory distress syndrome; amiodarone; cardiac surgery; pulmonary toxicity

**Abbreviations:** APT = acute pulmonary toxicity; AIPT = amiodarone-induced pulmonary toxicity; DEA = N-desethylamiodarone

Amiodarone is the one of the most commonly prescribed anti-arrhythmic agents worldwide.<sup>1</sup> Although initially developed as a new class of anti-anginal vasodilator, its derivative, desethylamiodarone, proved to be a powerful antiarrhythmic agent with atypical class III Vaughan-Williams properties, provoking substantial clinical interest. Surprisingly, almost all arrhythmias, whether atrial or ventricular in origin, in almost all patient groups ranging from myocardial infarction/heart failure to sudden cardiac arrest and postresuscitation scenarios, have benefited from amiodarone.<sup>2</sup>

Enthusiasm for this excellent agent has been tempered by its well-recognized side effects, the most feared being pneumonitis and fibrosis. The

incidence of such chronic pulmonary sequelae has been reported, in the early amiodarone era, to be as high as 1% in patients using amiodarone for a year, with a cumulative risk of 5 to 10%.<sup>3-6</sup> In addition, there is increasing concern over the role of amiodarone in the development of acute pulmonary toxicity (APT)/ARDS types of lung injury in severely sick surgical patients. The central theme of this article will be to explore the validity of this concern.

### PATHOLOGY OF AMIODARONE-INDUCED PULMONARY TOXICITY

Amiodarone's more notable properties include its unusually long half-life of > 30 days and its rather slow onset of action. Over time, amiodarone's principal metabolite, desethylamiodarone, accumulates in peripheral tissues, providing a sustained release reservoir and contributing to therapeutic serum concentrations. Thus, despite amiodarone's intended therapeutic target being the heart, amiodarone con-

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centrations measured in unfractionated pulmonary parenchyma significantly exceed that of the heart.<sup>7</sup> Accumulated concentrations of amiodarone's derivative in particular lung compartments, such as the type II pneumocyte, further exaggerate this effect. Furthermore, the route of administration is important as amiodarone accumulates more rapidly in the lungs of patients receiving IV therapy.<sup>8</sup> Amiodarone's pulmonary toxicity may be related, at least in part, to excessive lung concentrations.

Though several competing mechanisms have been proposed to explain this pulmonary toxicity, there has been little conclusive evidence supporting any of these suggestions. The two most prevalent hypotheses are variations on the themes of adaptive-immune-mediated hypersensitivity and direct drug-induced phospholipidosis.<sup>9</sup>

To identify clues for a definitive pathophysiological explanation, amiodarone pneumonitis has been extensively investigated histopathologically. Affected lungs manifest changes ranging from lipid infiltration of endothelial and type II pneumocytes (thought to reflect a disturbance in lung phospholipid turnover), cellular infiltration of the alveolar spaces by foam-laden macrophages, and, in a proportion of cases, septal thickening with or without mononuclear cell infiltrates to frank fibrosis.<sup>10</sup> One notable difficulty with the interpretation of this heterogeneous pathological picture is the failure of the literature to make a clear distinction between APT/ARDS and chronic lung injury. The reason for this is that the pathological findings are considered by many to be heterogeneous manifestations of a single disease process. It has also been suggested that the occurrence of the ARDS, a common condition in the postsurgical setting, may often mask the underlying lung amiodarone-induced pulmonary toxicity (AIPT), causing it to remain underrecognized.

Another complicating factor is that cell infiltrates within the alveolar space, harvested by BAL, are of variable descent and, in addition to macrophages, include neutrophils and lymphocytes. Unlike other parenchymal lung diseases, the pattern of infiltrate does not correlate in any consistent way with either the disease entity or with the prognosis.<sup>11</sup> For example, the inconsistent presence of neutrophils would normally militate against a strict diagnosis of an acute lung injury. Thus, despite the heterogeneity of the cellular infiltrates, and despite the evidence from histologic specimens and experimental data identifying only the macrophage as a consistent and important target for acute amiodarone toxicity, the other cellular elements may modify or contribute to the overall presentation of amiodarone dependant disease.<sup>12</sup>

## CLINICAL MANIFESTATIONS AND RISK FACTORS FOR APT

Although the pathologic features of chronic lung damage by amiodarone were first reported in the early 1980s and are now familiar to clinicians, the inclusion within these reports of some patients who had rapidly progressive courses was, essentially, not noticed. Particularly in the ICU setting, amiodarone's role in acute lung injury has been poorly appreciated.<sup>13-15</sup>

Attempts to identify risk factors for chronic lung complications, and hence to rationalize prescribing amiodarone, led clinicians to conclude that elderly patients with preexisting pulmonary disease, on doses of > 400 mg/d, were at the greatest risk of chronic pulmonary toxicity.<sup>16</sup> It was believed that pulmonary fibrosis was related to the cumulative dose of amiodarone, with total doses of 140 to 230 g being associated with a high likelihood of clinically significant lung damage.<sup>16</sup> Indeed, some studies suggest that those with preexisting lung disease are up to nine times more likely to develop chronic pulmonary toxicity.<sup>17</sup> Interestingly, as with a number of other pulmonary toxins, some investigators feel that reduced amiodarone excretion, possibly a genetically determined property relating to P-glycoprotein or to the cytochrome P450 superfamily, may also play a crucial role.<sup>9,18</sup> Despite these epidemiologic findings, amiodarone's lipophilic properties, which produce a high volume of distribution of around 5,000 L and a long half-life of around 30 to 108 days, lead to highly unpredictable serum concentrations. This, coupled with ignorance as to the mechanisms of its toxicity at differing parenchymal drug concentrations, has prevented any accurate prediction of risk being made from simple serum drug measurements.

A different set of risk factors may operate in acute amiodarone-mediated lung injury. APT was first recognized in 1985, when two patients developed fulminant and ultimately lethal lung injuries.<sup>19</sup> To understand why severe complications didn't affect the majority of patients started on amiodarone, the authors speculated that a process associated with pulmonary angiography, the only common factor in their patients, might have predisposed these two patients to severe reactions. Although a number of possible causes could have been invoked, it appeared that a concomitant or preexisting lung injury might render the lung liable to amiodarone's acutely toxic proclivities.

In early studies assessing the danger of amiodarone in acutely ill patients, researchers encountered a number of difficulties. One obvious difficulty with testing the above hypothesis was determining

whether the lung pathology that occurred was coincidental. It is plausible that patients with significant pulmonary injury and with tendencies to acute lung injury are less stable and more prone to cardiac arrhythmias, and are, therefore, more likely to require amiodarone, hence the association of APT with amiodarone use. A further complication in resolving this question can be attributed to the difficulty of extracting data retrospectively from a heterogeneous collection of patients in an ICU setting. Variations in primary diagnosis and treatment modalities, such as differing drug regimens, in an ICU setting represent variables that might not be easily dissected away from the patterns and responses to amiodarone use. Finally, the numbers of patients involved in these studies are usually small, and hence the studies lack the statistical power to make definitive conclusions, being particularly prone to type II errors. Strict adherence to the rules of evidence based medicine are not possible and, as an alternative, the Bamford Hill criteria should be invoked.<sup>20</sup> These criteria guide the assessment and acceptance of biologically plausible findings from a number of studies that, when pooled, are found to be robust under different clinical conditions, when derived from different centers, possibly from different countries, and that indicate a similar dose-dependent response trend.<sup>20</sup> To fulfill these criteria, we will explore the existing data to determine if these criteria are met, and we will then present a biologically plausible argument for acute AIPT.

There were suggestions early on from the literature that amiodarone toxicity could be manifest as early as 4 weeks after initiation of therapy.<sup>21,22</sup> Subsequently, small case studies reported APT in patients treated with amiodarone. These initial reports concentrated on patients who had already been diagnosed with chronic pulmonary amiodarone toxicity, exacerbated by surgery, resulting in acute respiratory failure.<sup>23</sup> These studies suggested that, in lung-diseased patients, the effect of all surgical insults, particularly from thoracic interventions, synergized with amiodarone and resulted in acute pulmonary responses and mortality. Only later were similar responses reported in patient groups with no previous evidence of pulmonary damage.<sup>23-25</sup> These early reports stimulated a prospective comparison between 28 surgical patients treated with amiodarone and a control group. A significant increase in respiratory failure (four in the amiodarone group vs zero in the control) and morbidity was demonstrated in those on amiodarone.<sup>26</sup>

Greenspon and colleagues<sup>27</sup> presented a much larger series of patients, undergoing cardiothoracic surgery, who were retrospectively analyzed for different patterns of amiodarone use. They demon-

strated that, out of the total 67 patients, 9 of 18 patients (50%) being treated with amiodarone and who survived surgery developed ARDS. This was distributed to 3 of 9 patients with recent amiodarone loading (doses of 1200 mg daily) and 6 of 9 receiving amiodarone long-term. Significantly, none of the surviving 44 amiodarone-free patients fulfilled the ARDS criteria.<sup>28</sup> The patients had no differences in their preoperative and intraoperative clinical parameters. It was concluded, therefore, that patients undergoing cardiac surgery might be particularly likely to develop ARDS if receiving amiodarone. However, even though the patients were selected consecutively, the main weakness of this study was the retrospective nature of this and other analyses.<sup>29,30</sup>

A later trial, where amiodarone was used as prophylactic treatment for supraventricular tachyarrhythmias after pulmonary surgery, confirmed and expanded the view that lung injury, be it caused by surgery or anesthesia, interacts with short- or long-term amiodarone therapy by increasing the risk of ARDS.<sup>30</sup> Amiodarone was given IV in conventional doses (150 mg IV < 1 h after surgery, followed by 1,200 mg IV for 3 days). Out of 32 patients undergoing pneumonectomy, three developed ARDS (two on postoperative day 2, the other on postoperative day 3), for which no cause could be implicated other than amiodarone. Amiodarone levels were similar in those who developed ARDS when compared with those who did not. Two of these patients died. These adverse findings prompted a retrospective analysis examining the relationship between postoperative ARDS and amiodarone usage. The incidence of ARDS was 11% in those treated with amiodarone and 1.8% in those not treated ( $p < 0.0001$ ). The authors concluded that, among patients receiving amiodarone who developed ARDS after lung surgery, amiodarone was a critical factor. Confirming this worrisome data was a retrospective review of 10 patients who had died in the ICU from ARDS and who were examined postmortem.<sup>31</sup> Seven had received amiodarone, three for > 48 h. These latter three patients had widespread histologic evidence of lipoid pneumonia, presumably from amiodarone. This study suggested, therefore, that amiodarone as a significant contributor to ARDS in the ICU setting may be much more common than previously appreciated.

The strength of the studies quoted above are their robustness under different clinical conditions, as lung pathology occurred from diverse thoracic stimuli and in different centers. Similar studies, in the different setting of heart transplant patients, once again demonstrated that perioperative amiodarone use for > 4 weeks is associated with higher 1-month

posttransplant mortality for reasons which, though unspecified, may be related to APT.<sup>32</sup> The variation in susceptibility and, hence, attempts at risk stratification in ICU-related acute APT/ARDS in these studies maybe ascribed in part to the variation in lung concentration of amiodarone (which in turn may relate to the oral dosage, pattern of metabolism, and whether IV therapy has been used). The variation may also be explained by the variation in oxygen usage or underlying degree of lung damage.<sup>33,34</sup> The duration of amiodarone therapy *per se* does not, however, explain the variation in the incidence of amiodarone-related ARDS.

These amassed studies have raised significant concerns that amiodarone may contribute toward morbidity and mortality in an ICU setting. At present, however, the data presented do not constitute a definitive evaluation of the role and the magnitude of harm to patients benefiting from amiodarone use at the time of cardiothoracic surgery. Ideally, to assess the true incidence of amiodarone-induced or -exacerbated ARDS, the large, randomized, blinded, prospective clinical trials examining the role of amiodarone in the prevention of conditions such as postcardiac surgery atrial fibrillation should be analyzed.<sup>9</sup> In certain atrial fibrillation prevention trials, amiodarone has been administered "on the pump" or postoperatively, a timing that may miss the critical period for amiodarone-induced lung injury.<sup>35,36</sup> Although they suggest that amiodarone in this setting is not associated with harm, these studies have involved only small numbers. Although amiodarone was given preoperatively in other trials, again only small numbers were involved. For example, in one such trial, where patients received 4.8 g amiodarone prior to surgery, a small, nonsignificant increase of 3.8% in serious morbidity/death was reported in the treatment group.<sup>37</sup> This sort of data in itself, given the small numbers involved, neither confirms nor denies amiodarone safety.<sup>38</sup> Furthermore, such trials often exclude sick patients and concentrate on elective cases, excluding those most likely to require amiodarone, who are those most likely to develop APT/ARDS and those for whom amiodarone may be the most harmful. For example, large trials of postmyocardial infarction or heart failure patients, who were treated with amiodarone, from which one might also seek data, had rather small numbers of patients undergoing elective and particularly emergency cardiac surgery, making the assessment of ARDS statistically ambiguous.<sup>39-41</sup> For these reasons, we are concerned that, in sick patients, acute amiodarone pulmonary toxicity may be more common than realized, and we suggest that clinicians should continue to be cautious in using this drug in the ICU setting.

## MECHANISM OF ACUTE AMIODARONE-MEDIATED LUNG INJURY

Because of its intimate relation with an often noxious environment, the lung has evolved a highly dynamic and sophisticated immunologic response. A cardinal feature of this rapid-response inflammatory system is the existence of a powerful regulatory counterinflammatory system. Although, under resting circumstances, the lung appears to be static from an inflammatory standpoint, there are in fact two active and competing systems in equilibrium. When the lung is subjected to a local insult, for example by a pathogen, this balance is locally perturbed. The inflammatory response is thus activated, and the damping antiinflammatory response is inhibited. This kinetically amplifying effect of both activating and releasing opposing systems may be critical in patrolling the large, susceptible surface of the lung in response to ever present and rapidly acting microbial threats. The system is prone to hypersensitivity, especially in the context of an insult that is unusually diffuse in nature and for which this powerful lung response has not evolved. In this context, an unbridled inflammatory response is activated throughout the lung, compromising ventilation:perfusion properties of the lung. This is reminiscent of ARDS, a characteristic response to viruses, chemicals, and humoral mediators that have an ability to excite diffuse immune responses within the lung.<sup>28</sup>

Though it is possible that amiodarone toxicity is triggered by synergy with focal sepsis and then either remains localized or becomes generalized, it seems more likely that amiodarone produces a diffuse lung injury in most cases. The insult may be a direct toxic effect of amiodarone (for example, from the release of active iodide species), from an immunologic influence of the drug, or more interestingly, from a free radical effect.<sup>42,43</sup> Free radicals are derived from amiodarone's influence on mitochondria and the well-recognized NADPH oxidase family of pulmonary and immunologic enzymes that synthesize superoxide anions involved in defense and lung signaling.<sup>44,45</sup> This effect may be exacerbated by the influence of high oxygen partial pressures that synergize with amiodarone-induced radicals to increase lung damage.<sup>46</sup> Physiologic and genetic studies may further elucidate the role of superoxides in lung injury and, in the future, may help to identify patients particularly at risk by, for example, identifying patients with activating polymorphisms in NADPH oxidase subunits or inactivity in superoxide dismutase who are particularly prone to lung injury.

By providing the lung with an excess and unchallenged superoxide load in both short- and long-term treatment settings, amiodarone may precipitate lung

injury and thus cause long-term damage.<sup>47,48</sup> In the short-term context of surgery, particularly cardiac surgery, a number of synergistic elements may also be present. The presence of high concentrations of oxygen in the lung coupled with the damage of intubation/ventilation, surgical trauma (especially in the thorax), and systemic inflammatory responses induced by cardiopulmonary bypass (responsible for “post-pump” syndrome) may relieve the lung of its antiinflammatory influences and, in the context of high superoxide radical concentrations from amiodarone, may induce ARDS.<sup>31,49–53</sup>

Alveolar macrophages exposed to amiodarone generate functionally significant products such as superoxide and fibronectin, which have been implicated in lung fibrosis, and they do so more voraciously than their bone marrow-derived counterparts.<sup>12</sup> Furthermore, these macrophages develop characteristic lamellated cytoplasmic inclusions, a structural abnormality that some authorities regarded as diagnostic features of AIPT, until data became available showing that such findings also occur in those receiving amiodarone but free of adverse reactions.<sup>12,54–56</sup>

In addition to macrophage toxicity, amiodarone, and particularly its metabolite N-desethylamiodarone (DEA), are cytotoxic to lung fibroblasts, to endothelial cells, and to type II pneumocytes.<sup>57,58</sup> DEA is considered by some to be the principle toxic agent in lung toxicity, a contention supported by small studies, demonstrating that those with lung injury have very high DEA:amiodarone ratios (> 1.3, as opposed to the < 1.0 found in nontoxic patients).<sup>9</sup> The role of DEA has been further emphasized by the finding that its physical properties allow it to partition into lung tissue approximately five times more readily than the parent amiodarone itself.<sup>9</sup> Macrophage, endothelial, and pneumocyte toxicity thus synergize to produce lung damage.<sup>59</sup>

Amiodarone also significantly alters the milieu of cellular gene expression within the lung. Lung hydroxyproline (an index of fibrosis) and lung phospholipid, particularly phosphatidylcholine (an index of phospholipidosis), are substantially increased by amiodarone in hamster models of lung disease and are attenuated by protective amino acids such as taurine and niacin.<sup>60,61</sup>

There has been increasing interest in the role of an acquired response in amiodarone lung toxicity, with the demonstration that natural killer and T-cells are found in increased numbers in subjects with BAL and may be functionally active.<sup>62</sup> As in most immune responses, it is thought that these cells orchestrate the responses of the macrophages by providing the appropriate cytokine environment to allow macrophage activation and functional maturation, as man-

ifested by the up-regulation of oxygen-derived free radical secretion. This immunologically mediated oxidant injury hypothesis is one that has proved appealing, especially in view of data demonstrating attenuation of experimental acute lung injury in general and mediation of amiodarone by the antioxidant  $\alpha$ -tocopherol.<sup>59,63</sup> However, there have been studies that have failed to demonstrate a similar degree of salvage.<sup>64</sup> Curiously and confusingly, in addition to generating superoxide and other free radicals, emerging data suggest that amiodarone itself has significant antioxidant properties.<sup>43,47,65,66</sup> The interpretation of these data is currently unclear.

#### CLINICAL MANAGEMENT OF ACUTE AMIODARONE-MEDIATED LUNG INJURY

Acute adverse pulmonary reactions to amiodarone have protean manifestations, including inducement or exacerbation of ARDS or bronchiolitis obliterans organizing pneumonia and, at least theoretically, a worsening of bronchospasm (via  $\beta$ -adrenoreceptor blocking action) and heart failure (via the negative inotropic action of amiodarone itself and of the solvent used in intravenous preparations, Tween 80).<sup>67,68</sup> If acute amiodarone lung toxicity is suspected, how should the clinician respond, other than stopping amiodarone? Unfortunately, there is little evidence either on how best to make the diagnosis or on how to intervene. The clinician thus frequently needs to rely on clinical skills rather than on conclusive diagnostic tests or proven therapies. Since acute amiodarone pneumonitis has not yet been adequately characterized, it is very difficult to know the “gold standard” for diagnosis. Proving that amiodarone, rather than other etiologies, is causing the ARDS or another acute pulmonary syndrome is usually achieved through exclusion. There is no typical plain film radiology, and high-resolution CT scanning appearances, so often helpful in chronic toxicity where heavy intrapulmonary deposits are seen, are not pathognomonic in acute disease.

Are BAL fluid findings helpful? The currently available data mainly relate to long-term rather than short-term amiodarone pulmonary toxicity, and they suggest that BAL findings are not particularly helpful. Early researchers believed that finding foamy (lipid-laden) macrophages in BAL fluid was diagnostic of amiodarone toxicity; unfortunately, it was later found that such findings also occurred in asymptomatic patients taking amiodarone.<sup>55</sup> Asymptomatic patients receiving amiodarone have increased BAL fluid cellularity, mainly due to macrophages.<sup>69</sup> In amiodarone pneumonitis, total cell BAL counts are raised compared with normal counts, but they do not

differ from those found in nontoxic patients.<sup>69</sup> Neutrophils and lymphocyte counts are often increased in amiodarone pneumonitis when compared to normal (or nontoxic amiodarone patients), but they do not differ from those receiving amiodarone who have interstitial pneumonitis for other reasons.<sup>69</sup> Lymphocyte subset typing suggests that lymphocytes are more likely to be CD8<sup>+</sup> than CD4<sup>+</sup> (*ie*, the CD4<sup>+</sup>/CD8<sup>+</sup> ratio is depressed); however, these differences are not sufficiently reliable as to be diagnostically useful.<sup>11</sup> Thus, total or differential BAL cell counts, while they may suggest the presence of pneumonitis, do not allow amiodarone to be directly implicated.

Likewise, lung biopsy, though it may be helpful and may show a characteristic lipoid pneumonitis, is more often nondiagnostic.<sup>11,54</sup> Unfortunately, the diagnosis is often made at postmortem examination.<sup>31</sup> If the diagnosis is made antemortem, the role of pulsed steroids is unclear, though they are often used.<sup>11,70</sup> Again, the data are mainly limited to the long-term situation, where there is some evidence that steroids are helpful. Amiodarone pneumonitis can recur if steroids are discontinued early on and can resolve in those given steroids who continue on amiodarone.<sup>14,71</sup> However, there are also widespread anecdotal data suggesting that chronic amiodarone pneumonitis can resolve satisfactorily without steroids. One case report, on chronic alveolitis associated with high levels of circulating immune complexes and a polyarthropathy, found that azathioprine and plasma exchange were useful, possibly acting in part by reducing immune complex levels and in part by reducing serum amiodarone levels, particularly DEA, albeit briefly given the high level of tissue binding.<sup>72</sup> The role of steroids in acute amiodarone pneumonitis is even less clear, though we suggest, empirically, that they may be useful given the very cellular nature of the infiltrate. Until unambiguous data are available, and given how sick these patients often are and how high their rate of mortality, the default position should be to give rather than not to give steroids. Given the paucity of data, we suggest that the management of this life-threatening condition might be best served by the establishment of a large, nationwide database on patients receiving and not receiving amiodarone in the ICU setting. This would help determine the actual danger of amiodarone in ICU and may help reveal useful therapies.

#### SUMMARY

In conclusion, there is evidence to suggest that patients who are subject to pulmonary insults may be

acutely susceptible to the harmful sequelae of amiodarone. More studies are needed to determine the level of risk and to identify factors that may minimize risk (*eg*, the pattern of amiodarone and oxygen use). Physiologic and genetic studies may, in the future, identify patients particularly at risk. Finally, the elucidation of the etiology of this lung damage may facilitate a concerted view of pulmonary damage and fibrosis caused by numerous pharmacologic agents.

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*Chest* 2001;120;275-282

DOI 10.1378/chest.120.1.275

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