To mark the 60th birthday of *Circulation Research* (1953–2013), the editors have commissioned *Circulation Research Classics*, a series of commentaries highlighting seminal articles published in the journal during the past 6 decades that have importantly shaped cardiovascular research. Written by leading experts, *Circulation Research Classics* are intended to describe the impact of these articles on the field by putting them in a historical perspective. The concept of classic is inextricably linked to time—a classic is something that maintains its value regardless of its age. Thus, an important consideration in selecting the articles to be highlighted is that they have stood the test of time, which is the most reliable indicator of the value of scientific work. By looking back at the illustrious past of *Circulation Research*, we hope to promote a deeper appreciation of the contributions of this journal to the advancement of knowledge.

Can We Do Better Than Dobutamine?

Elizabeth M. McNally

**Dobutamine: Development of a New Catecholamine to Selectively Increase Cardiac Contractility**

Tuttle & Mills


The development of dobutamine, an infusible inotropic drug for heart failure, was first described in 1975. Although this sympathomimetic was designed to increase cardiac output, it is far from ideal as a long-term safe strategy. New drugs for acute heart failure are needed, and the successful development of new approaches will require diverse expertise and resources.

In 1975, Tuttle and Mills¹ published in *Circulation Research* an article entitled “Dobutamine: development of a new catecholamine to selectively increase cardiac contractility.” This work, having been cited >600 times, ranks 54th on the list of most cited articles from *Circulation Research*. Working at the Lilly Research Laboratories, a part of Eli Lilly, Tuttle, a pharmacologist, and Mills, a medicinal chemist, systematically modified the structure of isoproterenol/isoprenaline with the goal of generating new drugs to improve cardiac function. It was known that isoproterenol, through its action on β adrenergic receptors, could increase cardiac contractility but did so at the cost of increased heart rate and a concomitant proarrhythmic effect. Moreover, the increase in blood pressure that occurs with isoproterenol infusion was felt to be less desirable in ischemic heart failure. The goal was to devise a compound with a reduced risk of arrhythmia by identifying compounds with less effect on increasing heart rate than the parent compound isoproterenol. The clinical target for this drug design was ischemic heart failure because, at the time, there was little available to treat acute heart failure of any form, and ischemic heart failure was most common. In the process of modifying the structure of isoproterenol, dobutamine was identified and remains to this day, one of the few drugs available to treat acute heart failure. Albeit imperfect, dobutamine continues to be a mainstay in the management of acute congestive heart failure and has been for 35 years.

To achieve the synthesis and testing of dobutamine, Tuttle and Mills tested 20 different compounds. As a benchmark, their preclinical evaluation also included known agents, such as norepinephrine and epinephrine. Beginning with the parent compound isoproterenol, the side chain hydroxyl group was removed, and this modification was associated with a positive chronotropic and inotropic effect (Figure). By working with additional substitutions of the side chains, the positive inotropic effect was favored by targeting β1 adrenergic receptors. This synthesis allowed for the development of a compound that increased cardiac output with comparatively less effect on chronotropy and, therefore, a reduced arrhythmic risk. In the process of synthesis and testing, it was critical to avoid compounds that would promote norepinephrine release to further reduce the arrhythmogenic properties. Because it was felt that many patients with heart failure were variably depleted of norepinephrine, stimulating norepinephrine release was to elicit unpredictable side effects.

The first pass screen involved testing compounds, including dobutamine, in feline papillary muscle preparations because this was a preferred model for measuring contractility. It was in this setting that it was observed that removing the hydroxyl group resulted in similar positive inotropic effects to isoproterenol without the same effect on heart rate. Contractile potency was compared among the different agents, and in vivo testing was performed in mongrel dogs. Some compounds were found to have vasodepressor effects and others had marked pressor activity. Dobutamine was found to have very slight pressor activity, only at higher doses, but this pressor effect was felt to be minimal. Because many patients with heart failure, particularly those with ischemic heart failure, required blood pressure lowering, compounds with less pressor effect were preferred.

The synthesis of dobutamine, its testing and reporting were remarkable on many levels. The scope of work described in the 1975 *Circulation Research* article was extremely broad. The authors not only describe the chemical synthesis of multiple compounds and the rationale but also described in detail...
Figure. The structures and effects of isoproterenol and dobutamine.

the in vitro testing using the papillary muscle system and the justification for advancing specific the specific compound, dobutamine, to in vivo studies and clinical use. Despite its effect and wide use, dobutamine has not fared well when examined in clinical studies, where it has been associated with increased mortality especially with longer term use.2,3

What is even more remarkable is the timing of when these experiments were being conducted. Tuttle began working with Mills on the development of dobutamine in 1968. At this time, the molecular detail of the adrenergic receptor system was not known, and the existence of distinct subset of receptors was even doubted by some. The 2012 Nobel prize in chemistry was awarded to Drs Robert Lefkowitz and Brian Kobilka for G-protein–coupled receptors. In Dr Lefkowitz’s Nobel acceptance speech, he cites publications from 1973 questioning the existence of α and β receptors.4 Dr Lefkowitz goes on to describe several of the first radioligand studies used to confirm the presence of distinct receptors.5,6 The work of Tuttle and Mills was conducted before the radioligand studies and rested entirely on the pharmacological observations. In their Circulation Research article, Tuttle and Mills noted “As currently classed, β1-receptors mediate the cardiac effects of adrenergic drugs, α receptors mediate vasoconstriction, and β2 receptors mediate vasodilation”7 and used this for the basis of their work, steering clear of the controversy surrounding the molecular identification of the targets of their drug and resting more on the in vitro and in vivo characterization of its effect.

Tuttle and Mills worked on the development of dobutamine from 1968 to 1974. Thus, they were developing dobutamine in the absence of clear data about its target(s), essentially using a blind approach to drug development. Abstracts describing some components of the dobutamine discovery were first presented in 1973 and 1974, and a new drug application was made to the Food and Drug Administration in 1971.8,9 Samples of the new drug along with the written description of the work had also been distributed to clinical investigators before the Circulation Research publication. A patent describing the synthesis and portions of the in vivo work documenting dobutamine’s efficacy was initially filed in 1972. That specific patent was abandoned and a new patent was filed in 1975 and granted in 1976 for dobutamine and its application to the treatment of heart failure.10 Lilly released Dobutrex in 1977, and dobutamine remains in common use for heart failure to this day.

Perhaps the most remarkable aspect of the Tuttle and Mills article is how very unlikely it would be for dobutamine to be developed and marketed in the current era. Only 2 years elapsed between the publication in Circulation Research and drug approval, a particularly short timeline from preclinical data and demonstration of clinical efficacy. In <10 years, dobutamine was synthesized, tested in the preclinical setting, and approved for clinical use. Whether this short timeline was because of the efficacy of dobutamine or the relatively simplicity of the approval process or both is not obvious. That it would be far less likely to happen now derives from a complexity of issues from limited pipelines and interest by large pharmaceutical companies, as well as a far more challenging drug approval system.

The development of new drugs for cardiovascular diseases, and especially for a disease like heart failure, is insufficient, despite profound unmet medical need. In 2009, heart failure was listed on 1 in 9 death certificates, and heart failure was responsible for >1 million hospital admissions in the United States.11 Overall, the 5-year death rate after a diagnosis of heart failure diagnosis remains at 50%, and the cost associated with treating heart failure in the United States is ≈40 billion per year. Since 1995, there has been no significant decline in heart failure, reflecting the absence of new medical developments for its treatment.12

The challenges around new drug development for heart failure are many. First, cost is paramount. In 2003, DiMasi et al13 surveyed pharmaceutical companies and it was estimated that the cost of new drug development was >800 million dollars in the year 2000. Using the DiMasi data, estimates for the costs of new drug development in current dollars far exceed a billion dollars per drug. Writing for Forbes in 2012, Herper14 provided an accounting that the cost of new drug development was even higher. He also recounted that an Eli Lilly executive compared the cost of new drug development to the cost of 371 Superbowl ads or the entire salary of the National Football league players for 1 year.15 Using current estimates, the cost of developing a single new drug development is ≈5% to 10% of the annual National Institutes of Health budget.

The risk associated with developing drugs for heart failure is also a deterrent because patients with heart failure have significant mortality and morbidity, and risk makes heart failure a less attractive target. Heart failure trials are complicated by the heterogeneous nature of heart failure cohorts. Typically, heart failure is largely lumped into a single entity, where individuals may have very distinct clinical courses. Most new drugs for cancer are targeted to specific types of cancer with precise molecular pathogeneses, and therefore the average heart failure trial differs considerably. The heterogeneous nature of heart failure may make it harder to see efficacy and, at a minimum, requires large populations to see effect. Larger trials are more expensive. Better approaches to heart failure may need to begin by better classifying and stratifying subtypes of heart failure, which require better diagnostics. For example, strategies aimed at improving molecular motor function, calcium handling, or stress signaling may be more effective in subtypes of heart failure but not others.

As may be expected from cost and risk analysis, there has been an overall decline in the number of patents by large pharmaceutical companies reflecting a decrease in research efforts.
In 1975, when dobutamine was developed, Eli Lilly filed 112 patents. In the most recent year for which data are available (2012), there were only 67 patents, and of those only 2 were awarded. This decline is typical of many large pharmaceutical companies. Patent filings have increased from device companies, reflecting electrophysiology devices, and mechanical circulator support. However, there remains considerable reticence around the cost of such therapies. Together these data support that it would be unlikely that in 2013 that large pharmaceutical companies would be pursuing research to discover a new compound like dobutamine.

Other models need to be used to develop new targets and to translate new discovery to improve health care, especially around heart failure. Year over year, there has been an increase in patent filing from academic entities in all areas, and occasionally there has been substantial windfall associated with patent licensing or royalties for a small number of institutions. The number of patent applications should have a positive correlation with spending on research, and research and development budgets should have some relationship to spending on health care. In 2012, total US government spending was $3.7 trillion dollars, but only $140 billion was spent on all science and technology with only 25% on biomedical R&D. With health spending at 3 trillion dollars, there are those who would suggest, from a business perspective, that research and discovery should be a greater fraction of the budget and that the 30 billion dollars invested by the National Institutes of Health is woefully insufficient. There should be balance in R&D spending between the public and the private sectors. The decline in patent applications from large pharmaceutical companies reflects shifting priorities, and the possibilities that a new dobutamine would be discovered in 2013 are not likely.

To remain competitive, nonprofit entities, including academic institutions, may need to backfill what is not being done in the private sector. To fuel this investment may require that those entities that receive federal funding actually devote a proportion of those budgets toward protecting ideas developed by those research dollars. At a minimum, as researchers and peer reviewers, we can place greater value on developing ideas that are so unique as to be protected by patents. Whether academic institutions spend adequately on protecting ideas can be debated. What is clear is that the model under which dobutamine was developed is no longer present, and new approaches and new partnerships are required to find heart failure drugs better than dobutamine.

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**References**

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