

Electrostatics and Inhaled Medications: Influence on Delivery Via Pressurized Metered-Dose Inhalers and Add-On Devices

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The movement of inhaler-generated aerosols is significantly influenced by electrostatic charge on the particles and on adjacent surfaces. Particle charging arises in the aerosol formation process. Since almost all inhalers contain nonconducting components, these surfaces can also acquire charge during manufacture and use. Spacers and valved holding chambers used with pressurized metered-dose inhalers to treat obstructive lung diseases are particularly prone to this behavior, which increases variability in the amount of medication available for inhalation, and this is exacerbated by low ambient humidity. This may result in inconsistent medication delivery. Conditioning the device by washing it with a conductive surfactant (detergent) or using devices made of charge-dissipative/conducting materials can mitigate electrostatic charge. This review discusses sources of electrostatic charge, the processes that influence aerosol behavior, methods to mitigate electrostatic charge, and potential clinical implications. Key words: electrostatic charge, aerosol, metered-dose inhaler. [Respir Care 2007;52(3):283–300. © 2007 Daedalus Enterprises]

Introduction

Inhaled medication delivered in aerosol form is widely prescribed for the treatment of obstructive lung diseases, including asthma and chronic obstructive pulmonary disease.^{1,2} The pressurized metered-dose inhaler (pMDI) is a popular inhaler choice because of its convenience, portability, and efficiency, compared with jet nebulizer treatment.³ Spacers and valved holding chambers (VHCs) are so-called “add-on” devices widely used with pMDIs to aid in medication delivery by allowing aerosol plume expansion to take place before inhalation, so that the ballistic fraction normally ejected from the inhaler mouthpiece is retained by the device, rather than deposited in the oropharyngeal cavity.⁴ These devices therefore allow delivery

of therapeutically beneficial fine particles to the respiratory tract. VHCs, rather than open-ended spacers, are particularly useful for patients with poor inhaler technique, since the chamber is closed by the inhalation valve, thereby retaining the aerosol until the patient inhales the medication.⁴ Electrostatic charge acquired either by the aerosol when generated, or present on the electrically insulating surfaces of the inhaler or add-on device, decreases aerosol delivery.³ This review brings together an understanding of the fundamental processes that cause electrostatic charge, examines ways it can be mitigated, and considers the clinical implications.

Data Location and Selection Methods

In the literature search for this review, relevant clinical and laboratory investigations were identified via the PubMed database, with the following key-word combinations: electrostatic, inhaler; electrostatic, spacer; electrostatic, holding chamber; antistatic, spacer; antistatic, holding chamber. In addition, relevant papers not included in PubMed were systematically searched back to 1994, including the biennial series of Respiratory Drug Delivery conference proceedings and the series of Drug Delivery to the Lungs conference proceedings published annually by the United Kingdom Aerosol Society.

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Electrostatic Charge: Fundamentals

In its simplest form, electrostatic charge represents either a surfeit of electron density (arbitrarily assigned as negative charge) or a corresponding deficit (positive charge) on a particle or surface. The presence of unipolar charges therefore reflects the predominance of either positive or negative charges, whereas bipolar charges define the presence of both signs on the particles or surface.⁵ Most aerosol particles carry some electric charge, and for highly charged particles the electrostatic force can be thousands of times greater than the force of gravity, associated with sedimentation.⁵ Apart from the effect on medication delivery from pMDIs and add-on devices, which is the focus of this review, computational models in which particle mobility through the airways of the respiratory tract has been calculated predict enhanced lung deposition of charged particles by increasing attractive forces.^{6,7} This prediction is supported by limited experimental work with nonconducting carnauba wax particles.^{8,9}

There are 3 mechanisms by which aerosol particles can acquire charge:⁵

1. Static electrification, whereby charge transfer takes place as each particle is separated from the bulk material or removed from a surface with different triboelectric properties¹⁰
2. Diffusion charging, where random collisions between particles and unipolar ions cause charge accumulation on the particles
3. Field charging, where particles acquire charge from collisions with unipolar ions in an applied electric field

Diffusion and field charging are seldom encountered in inhalation therapy, except with specific liquid electrohydrodynamic atomization systems, in which an applied electric field is used to charge the liquid stream containing medication emerging from an orifice or series of orifices. This process overcomes surface tension, causing the liquid filament to break up into droplets of well-defined size, depending on the operating conditions.¹¹ On the other hand, static charging is a widespread phenomenon. It may be further subdivided into (1) contact charging, where there is an initial attachment between particles or particle-surface touching, followed by separation without rubbing together, and (2) frictional charging where relative movement of the 2 surfaces takes place while still in contact.¹² In practice, however, it is difficult to distinguish the 2 processes, and the term “triboelectrification” is therefore often applied to include both forms of static electrification.¹⁰

The processes of charge acquisition and transfer associated with aerosol formation are highly complex and poorly understood. This is partly because contact charging is only well defined mechanistically in terms of differing work functions for metal-metal interactions associated with electrically-conducting surfaces.¹² However, most solid parti-

Table 1. Triboelectric Series for Polymers Used in the Manufacture of Inhalers

Polymer	Series order
Polystyrene	Positively charging
Polyethylene	
Polypropylene	
Polyethylene terephthalate	
Polyvinyl chloride	
Polytetrafluoroethylene	Negatively charging

cles formed from inhalers are poor conductors or electrical insulators¹³ whose surfaces are difficult to characterize and whose electron energies are ill-defined.¹² Furthermore, surfaces associated with inhaler components, such as valve elastomers,¹⁴ mouthpiece, canister holder, and add-on device,¹⁵ are almost always thermoplastic polymers that are electrical insulators, or, in the case of metal canisters in pMDIs, may have surface coatings that are insulating.¹⁶ Triboelectric series have been developed to assist in describing the likelihood of electron transfer between materials with different dielectric constants, since the substance with the higher dielectric constant is more likely to donate electrons to the other and thus become positively charged.¹⁷ Table 1 shows an example of such a series, for the polymers often used to manufacture inhalers.¹⁸ Note that such a series is only relevant to a specific set of experimental conditions, particularly relative humidity. In practice their value is limited, because the electrical properties of the materials used with inhalers, in particular the dielectric constants of particles containing medication, are usually unknown, triboelectrification is sensitive to ambient relative humidity, and surface treatments can have a major impact on the electrical behavior when the airborne particles make contact with adjacent surfaces.¹⁰

Measurement of Electrostatic Charge

In general, both static and dynamic methods have been used for the measurement of electrostatic charge.¹⁹ Static methods, in which no applied electric field is present, have been more widely used in characterizing inhaler-generated aerosols, in particular pMDI aerosols,²⁰ although the more recently developed dynamic methods, in which an applied electric field is present, are of increasing interest.¹⁹

A simple static method involves the use of an electrically insulated field-sensing probe that senses the presence of nearby surface electrostatic charge as an induced voltage. Such electrostatic volt meters or field meters are intended to determine charge without making contact with the surface, which would perturb the measurement by allowing charge transfer from the surface to the probe itself. They operate by driving the conductive housing of the

field-sensing probe to a voltage necessary to nullify the electric field between the probe and the surface. This condition is almost always achieved when the voltage on the probe matches the unknown voltage on that surface. By measuring the voltage on the probe, it is possible to deduce the equal voltage on the surface.²¹ Electrostatic voltage probes are therefore capable of rapidly determining the sign and charge intensity on surfaces, for instance within a nonconducting spacer or VHC.^{22–24} However, the physical size of the probe limits the spatial resolution of the method.

Static methods that involve charge collection and quantification have been widely adopted for measuring electrostatic charge of inhaler-produced aerosol particles.^{20,25–28} In the basic procedure that does not involve particle-size analysis, the entire aerosol is collected by passing the flow into a Faraday cage, which is a metallic housing within which the particles are deposited onto a filter.²⁹ Since it is the induced charge that is measured, the filter can be an electrical insulator. In the apparatus described by Peart et al, an electrical current is generated and measured by a sensitive electrometer.²⁸ Commercially available Faraday cup (well) electrometers typically have sensitivities that may be as low as 1 picocoulomb (pC), which appears to be adequate for measurement of most pMDI aerosols.²⁷ However, with the basic technique, only the total net charge can be determined, by integrating the area bounded by the instantaneous current-time curve that corresponds to the collection of the aerosol bolus. No information is collected concerning the more detailed relationships between the charge and size distribution of the aerosol particles.²⁰ Despite this limitation, early work by Peart et al, using a glass inlet induction port coupled to a single-stage impactor located immediately before the electrometer, so that only the fine particle fraction (percent of particles < 5.8 μm aerodynamic diameter, which are the most likely to reach the lower airways) was collected, provided insight into reproducible differences in electrostatic properties between various chlorofluorocarbon (CFC) propelled and hydrofluoroalkane (HFA) propelled pMDI formulations.^{27,28} That arrangement allowed them to assess the net charge of the fine particle fraction, rather than the overall charge of all the particles.

The electrical low-pressure impactor (ELPI) is a recently developed instrument that combines multi-stage inertial cascade impaction with quantification of the net charge associated with each aerosol particle-size fraction (Fig. 1). Ultra-sensitive electrometers (10^{-3} pC) connected to stages 1 through 12 act as a series of Faraday cups. The entry stage is not linked to an electrometer.³⁰ At the same time, it is possible for drug recovery to be made from the collection surfaces, as with a conventional impactor, thereby enabling direct traceability of aerodynamic particle size to mass of active drug substance.²⁰ The ELPI's

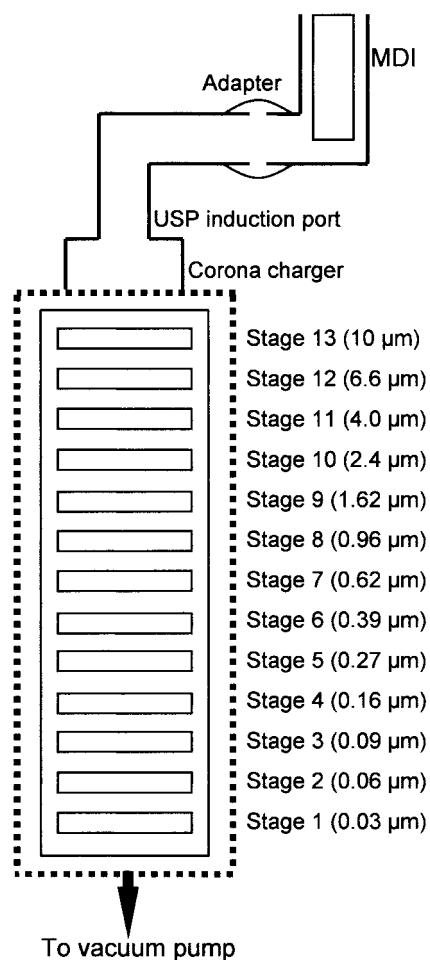


Fig. 1. Electrical low-pressure impactor modified to measure the electrical charge of a metered-dose-inhaler (MDI) aerosol. Impactor stages 1 through 12 are connected to sensitive (femtoamp level) electrometers. USP = United States Pharmacopoeia. (Adapted from Reference 20, with permission.)

performance evaluation was described by Marjamäki et al³¹; aerosol was sampled at a nominal flow of 10 L/min, providing 13 particle-size fractions, in the range 30 nm to 10 μm . The version of the ELPI used for characterizing pharmaceutical aerosols is normally operated at 30 L/min. In the original application of the ELPI, a unipolar corona charger, operated at +5 kV, was located at the entry to the impactor (see Fig. 1), so that the incoming particles were charged to a well-defined level before being size-fractionated. The detected charge level of each electrically insulated impaction stage related to the particle size, which provided a complete particle-size distribution when data from all the stages were considered. In the more recently introduced alternative mode of operation the charger unit is removed to measure the innate aerosol electrostatic properties, since otherwise artifact data can be created by contact charging processes.^{20,32} Charged particles passing through a given stage will produce a temporary image

charge. However, Moisio³³ showed that as a positively charged particle not captured by inertial impaction enters and exits an ELPI stage, a positive current peak is followed by a negative peak of equal magnitude, so that the net effect is zero. Hence, the electrostatic charge determined for each collection stage is associated only with the collected particles.

Although the ELPI has been quite widely used to provide charge/size profiles of pMDI aerosols, its calibration without the corona charger³¹ was recently questioned by Keil et al, as the result of the finding of systematic undersizing of a range of pMDI formulations in comparison with measurements made with a conventional Andersen 8-stage cascade impactor.³⁴ The ELPI was originally developed with the corona charger to detect the aerosol particles electrically, rather than by chemical analysis. The authors recommended that the ELPI be recalibrated without the corona charger, and they cautioned that ELPI particle-size data obtained without the charger should be regarded with caution, but they acknowledged that the ELPI can subdivide aerosols into 13 size fractions and provide specific mass deposition data, which, with the electrostatic charge data from the 12 lower stages, can be useful in product development. Note also that, since the charge detectors are Faraday cup in type, only the net charge, and not the distribution of charge, is measured for the population of particles represented by each size fraction.¹⁹

Dynamic electrostatic charge measurement methods involve particle movement in response to an applied electric field, and are an alternative to static charge-measurement procedures.¹⁹ Dynamic charge measurement methods operate on the basis that charged aerosol particles have finite electrical mobility in an applied electric field, which is a function both of particle size and the number of elementary charges attached to the particle of interest.³⁵ The charge distribution can be derived by comparing the electrical mobility distribution with the particle-size distribution determined by another method, such as inertial impaction.³⁶ Although widely used to measure aerosol particle-size distribution in environmental research, electrical mobility methods have seldom been applied with inhaler aerosols, possibly because they have generally been used to size particles after charging them to a known state,³⁵ rather than determining the intrinsic charge distribution of particles of known size. However, Balachandran et al recently described a technique by which bipolar charged particles are subjected to an applied direct-current electric field acting perpendicular to the axis of flow transporting the aerosol through the instrument, in a way that separates them on the basis of both polarity and charge magnitude.¹⁹ Their bipolar charge-measurement system provides fast, simultaneous measurement of the charge distributions of both polarities, for particles in the size range 1.0–10 μm , but it does not measure particle-size distribution, and to date the

system has been applied to the study of short-duration, rapidly evolving bolus aerosols from powder inhalers. This technique might also have use in characterizing pMDI aerosols, given that they are also formed as a short-lived bolus of particles following inhaler actuation.

A potential drawback with the bipolar charge-measurement system is that it requires making particle-size distribution measurements by another technique. The Electrical Single-Particle Aerodynamic Relaxation Time system (E-SPART, Hosokawa Micron Powder Systems, Summit, New Jersey) is a self-contained system that can measure particle size, albeit on a particle-by-particle (count) basis rather than a mass-weighted basis.³⁷ In the electrical excitation mode applicable to electrically charged particles, each particle entering the measurement zone is subjected to an oscillating electric potential; charged particles experience an oscillatory motion caused by the applied alternating-current electric field. This oscillatory velocity has a phase lag with respect to the applied field, and its measurement allows a determination of aerodynamic particle size by means of a laser-Doppler velocimeter. The amplitude of the oscillatory component of the particle motion is directly proportional to its charge, and there is a phase shift of 180° for particles with opposite charge polarity. This method has so far been applied (during the late 1970s and early 1980s) only to particle-size investigation of pMDI^{38,39} and nebulizer aerosols,³⁹ rather than as a technique for studying their electrostatic charge in addition to their particle-size distribution. The lack of more widespread use of this technique may be because it is an individual particle measurement technique, so it is more suited to measuring dilute continuously-generated aerosols rather than a concentrated, short-lived burst of particles from an inhaler.

More recently, Kulon et al described the simultaneous measurement of both aerosol particle size (via phase Doppler anemometry) and bipolar electrostatic charge distribution in an applied direct-current electric field, with a data-acquisition rate equivalent to more than 1,000 particles per second.⁴⁰ This instrument was used to investigate nebulizer droplets in the 1–10 μm size range, based on approximately 50,000 droplets per size distribution. Bipolar charge distributions were obtained at 4 discrete sizes (0.7 μm , 1.1 μm , 1.5 μm , and 1.9 μm), to study charge distribution as a function of size distribution. However, without a sophisticated sampling arrangement, the low flow (0.06 L/min) through the measurement zone (required to achieve laminar flow) may preclude using this method for pMDI aerosols at a flow similar to an actual respiratory flow.

Aerosol Formation in Metered-Dose Inhalers: Sources of Electrostatic Charge

pMDI formulations are normally either a micronized powder in suspension or a solution of the active ingredi-

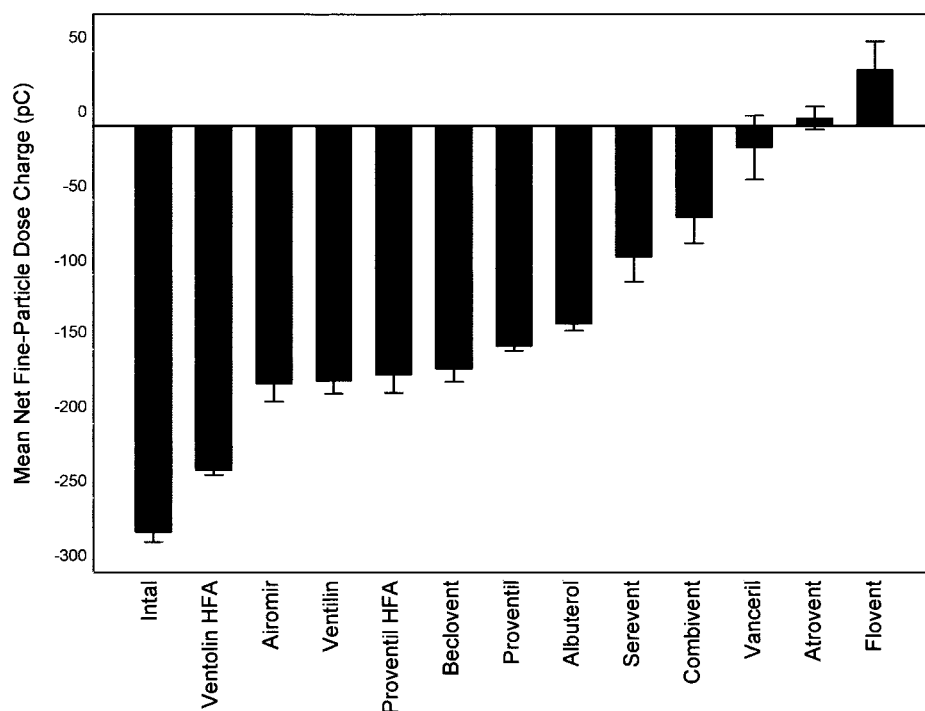


Fig. 2. Mean net fine-particle-dose electrical charge of aerosols from commercially available metered-dose inhalers. (Adapted from Reference 27, with permission.)

ent(s) in the propellant(s), and in some instances a co-solvent is also included.⁴¹ The process of aerosol formation, when the inhaler is actuated and the contents from the metering chamber are exposed to ambient pressure, is complex and depends on the vapor pressure of the propellant and the presence of solids, surfactants, and/or co-solvents.⁴¹ In general terms, the pressurized propellant flashes rapidly to vapor as it equilibrates with the ambient atmospheric pressure. This process provides sufficient mechanical energy both to eject the bolus of liquid from the actuator and to atomize the liquid. The droplets subsequently lose remaining volatiles by evaporation and become solid particles or liquid droplets that can be inhaled.

Atomization involves a form of static electrification often referred to as triboelectrification, in which charge separation occurs as the bulk liquid forms ligaments that break into droplets.¹⁰ There is controversy concerning the underlying physicochemical processes that charge the droplets,¹⁰ but all the proposed mechanisms involve the separation of negatively charged (anionic) species from positively charged (cationic) species near the surface of the liquid as the surfaces expand and new surfaces are formed during the atomization process.^{42–44}

Electrostatic charge is important with pMDI aerosols, both because of the processes during aerosol formation and because of subsequent particle-particle and particle-surface interactions. The nature of the container closure (canister and metering valve) affects the electrostatic charge

of the aerosol.²⁵ Water ingress into the canister via the elastomer compounds used as seals affects the net electrostatic charge of the aerosol,²⁵ and the formulation itself appears to have intrinsic electrostatic properties once atomized. Some of the new HFA formulations that have replaced their CFC predecessors appear to be associated with greater electrostatic charge.^{20,27} Peart et al studied the charge differences among various commercially available formulations. They used a sensitive electrometer coupled to a single-stage impactor acting as a Faraday cup, and in the fine particles found that the mean net charge per actuation ranged from -270 pC to $+45$ pC (Fig. 2).²⁷

More recently, Glover and Chan sampled aerosol with an ELPI at 30 L/min and found that various pMDI formulations have quite distinct and reproducible electrostatic-charge/size profiles.²⁰ For instance, the aerosol from 10 single actuations of an albuterol sulfate suspension formulation with HFA-134a propellant (Ventolin-HFA, 100 μ g albuterol base equivalent per actuation) had a net negative charge, irrespective of particle size. In contrast, a suspension formulation of fluticasone propionate in HFA-134a propellant (Flixotide 250 μ g/actuation) produced bipolar charged aerosols. Particles larger than 1.0 μ m aerodynamic diameter carried much of the mass of active ingredient and were negatively charged, whereas finer particles were positively charged. The mean net charge of the fine particles (< 6.6 μ m) was quite reproducible from actuation to actuation with inhalers that contained either for-

Table 2. Mean Charge of Fine Particles Per Actuation

Inhaler/Usage Lifespan*	Charge (mean \pm SD pC)	
	Ventolin	Flixotide
1 - beginning	-1,294 \pm 106	+486 \pm 28
2 - beginning	-1,052 \pm 37	+478 \pm 36
3 - beginning	-1,187 \pm 47	+554 \pm 21
1 - middle	-1,201 \pm 71	+504 \pm 31
2 - middle	-1,145 \pm 38	+503 \pm 51
3 - middle	-1,260 \pm 47	+560 \pm 31
1 - end	-1,228 \pm 78	+508 \pm 31
2 - end	-1,323 \pm 165	+529 \pm 38
3 - end	-1,341 \pm 145	+595 \pm 39

*10 actuations

pC = picocoloumb

Fine particles = $<6.7 \mu\text{m}$ aerodynamic diameter

(From Reference 20, with permission.)

mulation (Table 2). Although Glover and Chan observed a trend toward slightly increased charge magnitude during the inhaler's life, they indicated that a study with more inhalers is needed to confirm if that change is statistically significant.

Kwok et al extended the measurements of Glover and Chan by examining whether the manner in which the inhaler was used affected the aerosol's electrostatic charge.⁴⁵ They measured charge/size profiles of various pMDI formulations, delivered either as single, discrete actuations, each separated by 1 hour, or as a series of 10 so-called "continuous" actuations, each 30 s apart. Charge/size profiles were measured for several HFA formulations, including Intal Forte (5 mg/actuation cromolyn sodium in HFA-227), Tilade (2 mg/actuation nedocromil sodium in HFA-227), Flixotide (250 μg /actuation fluticasone propionate), Ventolin (100 μg /actuation albuterol sulfate), and Qvar (100 μg /actuation beclomethasone dipropionate in HFA-134a). The profiles of Intal Forte and Tilade were similar to that of Flixotide (Fig. 3), whether the actuations were delivered singly or in continuous mode. The data for Flixotide were also comparable with Glover and Chan's²⁰ Flixotide measurements. In all cases, particles larger than about 0.6 μm carried negative charges, and smaller particles were associated with positive charge. On a mass-weighted basis, negatively charged particles were therefore associated with the bulk of the drug mass, which in all cases was contained in particles larger than 1 μm . Although there was a trend of increasing positive charge with decreasing particle size in the range 0.2–1.0 μm with these formulations, little drug mass was present. However, the mean net charge of fine ($< 6.66 \mu\text{m}$) particles that contained both drug and excipient was positive (Table 3).

The charge/size profiles measured by Kwok et al for Ventolin were affected by the way the inhalers had been

used, in contrast with the behavior of Intal Forte, Tilade, and Flixotide.⁴⁵ When delivered "continuously" (30 s apart), the Ventolin profiles were unipolar and negatively charged (Fig. 4), similar to the behavior described by Glover and Chan.²⁰ However, the corresponding profiles became bipolar when the aerosols were generated by discrete actuations (separated by at least 1 hour) (see Fig. 4).

Bipolarity was also observed by Orban and Peart⁴⁶ for single-actuation profiles, but they did not specify whether their measurements were made with CFC or HFA Ventolin. Keil et al also reported, from similar studies, that aerosols derived from single actuations of HFA Ventolin had bipolar profiles.³⁴ In both investigations, negative charge was associated with the sub-micron portion of the size distribution profiles, whereas the larger particles, which contained most of the mass of albuterol sulfate, were positively charged.^{34,45} Overall, however, the mean net charge associated with fine particles was negative.

Table 3 shows data from Kwok et al, who postulated that the high negative charge of the sub-micron particles may be due to their greater surface area per unit mass (specific surface area), which affords greater opportunity for charge accumulation from triboelectrification, resulting in higher specific charge (charge/unit mass of drug). Furthermore, after evaporation of propellant, these high charges may be associated with remaining non-drug-containing excipient particles and impurities, such as water. The contribution of excipients to the charge on pMDI aerosols was alluded to in previous studies.^{20,28} Kwok et al further hypothesized that charge relaxation may influence the charging of albuterol sulfate in this formulation. Upon actuation, as electrostatic charges are produced on the particles, counter-charges must reside in the actuator, the metering valve components, and formulation residue deposited at those locations. These counter-charges take time to decay, and their presence may therefore affect charging of particles in a subsequent actuation, if timed shortly afterwards.

Unlike the suspension formulations just mentioned, Qvar is a solution formulation of beclomethasone dipropionate with ethanol as co-solvent in the HFA propellant,⁴⁷ and no surfactant is present. Kwok et al reported that the aerosols generated from discrete actuations of Qvar were unipolar and positively charged, irrespective of size (Fig. 5),⁴⁵ which was subsequently confirmed by Keil et al.³⁴ Kwok et al found that Qvar's net fine-particle charge was both lower and more variable than that of Intal Forte, Tilade, or Flixotide (see Table 3). They pointed out that, in the Qvar formulation, because the drug is dissolved (not suspended particles), the mass of drug in any droplet is in direct proportion to the droplet size. They hypothesized that any charge contribution arising from the excipients would be directly associated with drug mass, which explains their observed correlation between specific charge (charge/unit mass of drug) and particle size. Since the Qvar aerosol

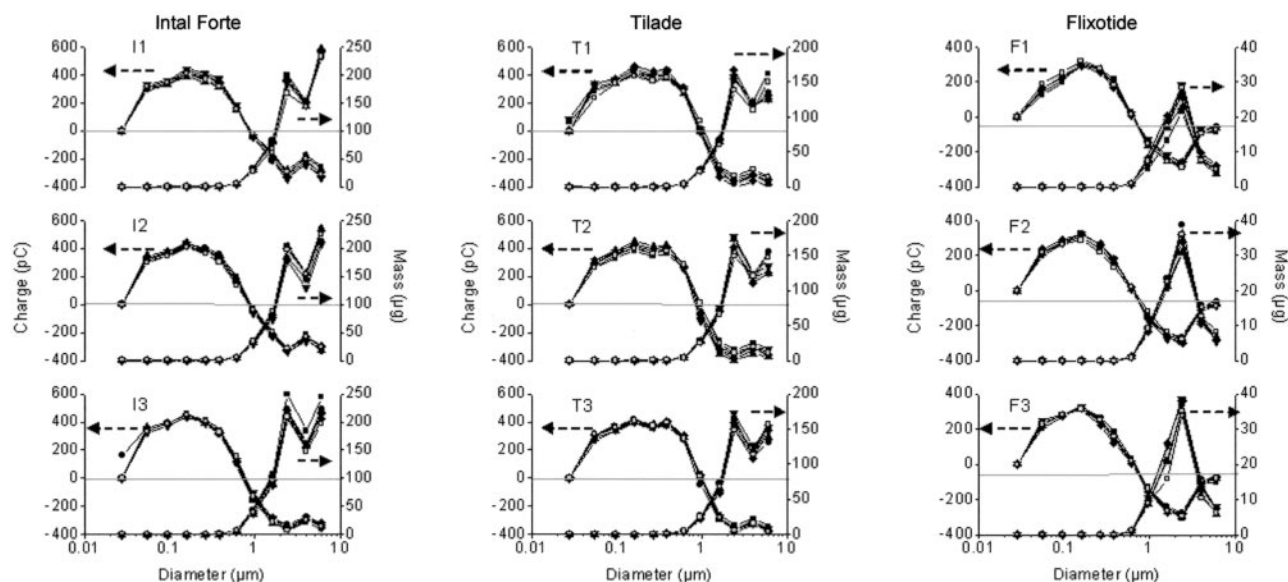


Fig. 3. Charge and mass of aerosols from 3 commercially available metered-dose inhaler formulations (Intal Forte, Tilade, and Flixotide) with "discrete" actuations (separated by more than 1 hour) (■, ●, ▲, ▼, and ◇ symbols) versus "continuous" actuations (taking place immediately after 10 actuations at 30-s intervals) (249 symbols) (From Reference 45, with permission.)

Table 3. Fine-Particle Mass and Associated Charge Per Actuation*

Inhaler	Formulation Type	Fine Particle Mass (mean \pm SD μg)	Charge (mean \pm SD pC)
Ventolin	Suspension	43 \pm 10	-1,100 \pm 220
Intal Forte	Suspension	480 \pm 43	+1,120 \pm 120
Tilade	Suspension	373 \pm 19	+1,150 \pm 80
Flixotide-250	Suspension	73 \pm 12	+450 \pm 30
Qvar-100	Solution	50 \pm 12	+290 \pm 230

*Fine particles were defined as those $<6.06 \mu\text{m}$ aerodynamic diameter in Reference 41, but should have been $<6.66 \mu\text{m}$, based on the calibration data from Marjamäki et al.³¹ There were 18 actuations (6 actuations from each of 3 inhalers). pC = picocolomb (Data from Reference 45.)

generated in the continuous mode was only lightly charged (see Fig. 5), they suggested that charge relaxation, as described for Ventolin, may also take place with Qvar, and commented that (unspecified) interactions between the drug and formulation and the materials of the metering valve and inhaler stem may be responsible for the charging process. A recent report compared the charge/size profiles of commercially available Qvar emitted with a Spraymiser valve and Qvar formulation re-packaged in a canister with a metering valve and stem made of nonconducting materials (polyester valve stem, EPDM [ethylene propylene diene monomer] elastomers, and a polyamide gathering ring), and the results showed the important effects of pMDI materials on aerosol electrostatic charge.⁴⁸ The nonconducting pMDI materials significantly lowered (1) the mean \pm SD charge, from $+448.6 \pm 235.9$ pC/actuation

($n = 3$ replicates) to $+175.03 \pm 56.2$ pC/actuation ($n = 9$ replicates), (2) the charge associated with each size fraction, measured with an ELPI, and (3) the fine ($<4.04 \mu\text{m}$) particle mass per actuation. Mean \pm SD mass decreased from $23.8 \pm 1.7 \mu\text{g}$ with the commercial Qvar product to $10.2 \pm 2.6 \mu\text{g}$ with the re-packaged Qvar formulation.

In summary, it appears that it is the propellant-drug combination, rather than the propellant itself, that determines the charge/size profile of these formulations.⁴⁵ Although data have been produced that demonstrate the wide range of electrostatic properties associated with commercially available pMDIs, as yet there have been no systematic investigations to link changes in electrostatic properties to specific attributes of the formulation or the inhaler components. Such studies will be necessary to develop measures to control and mitigate electrostatic charging with pMDIs.

Electrostatic Phenomena With Add-On Devices

Many studies have shown that the capability of a VHC to deliver medication efficiently and consistently is compromised by electrostatic charge.^{49–52} In addition to the electrostatic charge of the aerosol from the pMDI, the electrically insulating nature (low dielectric constant) of the polymers, such as polycarbonate or polyester, that are widely used in the manufacture of currently available devices, contributes to charge acquisition.^{49,53} These polymers acquire surface electrostatic charge by frictional contact with materials that have different dielectric constants, during their manufacture and use.⁵⁴ There is evidence that

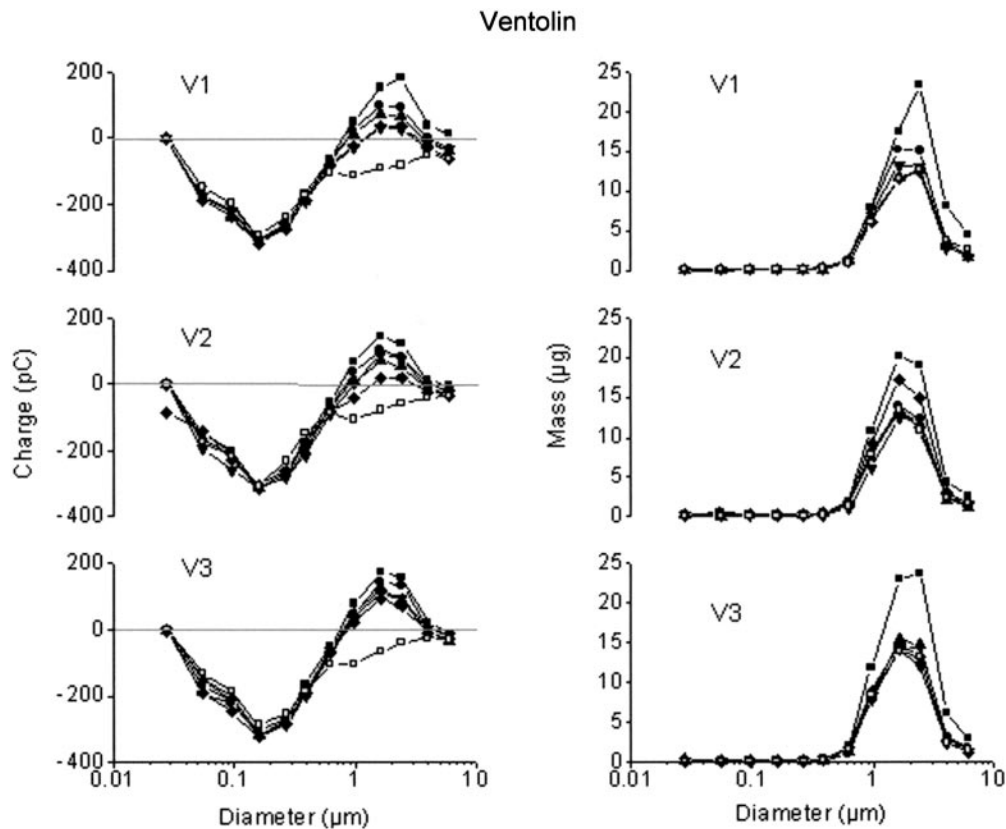


Fig. 4. Charge and mass of aerosol from 3 Ventolin inhalers (V1, V2, and V3) with “discrete” actuations (separated by more than 1 hour) (■, ●, ▲, ▼, and ◇ symbols) versus “continuous” actuations (taking place immediately after 10 actuations at 30-s intervals) (249 symbols). (From Reference 45, with permission.)

VHCs have discrete, localized, and separate regions of positive and negative charge, to judge from the variable measurements of induced electrostatic voltage profile (a measure of surface potential) made by Dewsbury et al, using a field-sensing probe in a large-volume (750 mL) polycarbonate VHC (Volumatic).²² Similar surface-charge behavior was recently found by Kwok and Chan, who reported a variation in induced voltage, ranging from about -50 V to $+1,600$ V, in a polyester-body VHC, which they rotated around a field-sensing side-view probe located midway within the chamber, with the inner wall of the VHC 3 mm from the probe (Fig. 6).²⁴

Since the incoming aerosol particles, which are probably also charged for the reasons already described, are confined within the volume of the add-on device, mutual repulsion due to their space charge (excess of electron density) causes them to move toward the walls.²⁷ Deposition then takes place due to (1) attractive (coulombic) forces between the charged particles and the oppositely charged surfaces, and (2) image forces set up by slight polarization of charge-neutral surfaces, by virtue of the close proximity of charged particles.⁵⁵

Loss of aerosol particles to the walls is both rapid and continuous, so the aerosol half-life within the device is

significantly reduced,⁵⁶ so the impact on medication delivery can be significant. Surprisingly, the relationship between the charge polarity of various formulations of incoming aerosol and the charge acquired by the add-on device has yet to be systematically studied, probably because the means for determining charge as a function of particle size have only become available in the past few years. Kwok and Chan have come closest to meeting that goal. They linked drug mass output and charge/size profile for 2 formulations (HFA Ventolin and HFA Flixotide) with and without a polyester VHC (AeroChamber Plus).²⁴ In both instances, drug output and magnitude of charge were highest when the pMDI was used alone. New (unwashed) VHCs were associated with significantly lower drug output and charge, and the shapes of the charge/size profiles were largely unaffected. Kwok and Chan hypothesized that the observed charge reduction (measured after leaving the add-on device) is associated with the neutralization of charge as particles of one polarity are attracted to oppositely charged locations on the VHC wall.

Traditionally, investigators have concentrated on measuring the loss of medication emitted from the VHC with a measure of electrostatic behavior made within the device, or have simply observed changes in emitted drug

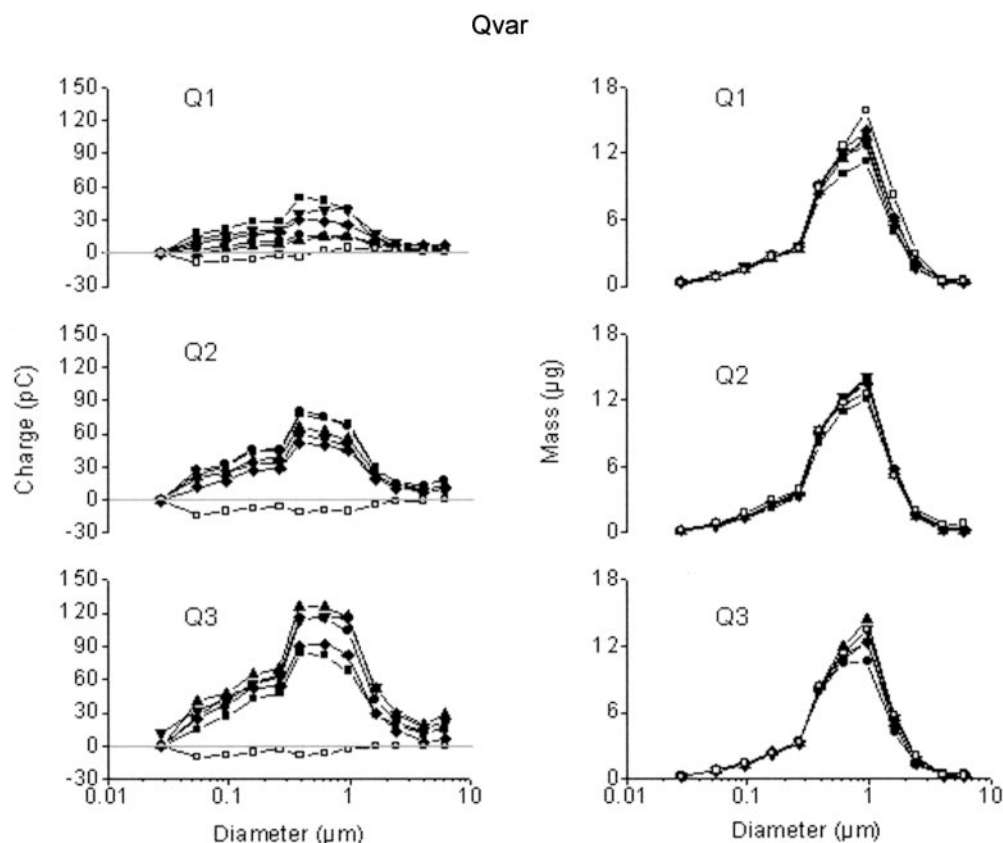


Fig. 5. Charge and mass of aerosol from Qvar inhalers (Q1, Q2, and Q3) with “discrete” actuations (separated by more than 1 hour) (■, ●, ▲, ▼, and ◇ symbols) versus “continuous” actuations (taking place immediately after 10 actuations at 30-s intervals) (249 symbols). (From Reference 45, with permission.)

mass following measures to reduce electrostatic charge. Thus, in the mid-1990s, Dewsbury et al were able to correlate changes in particle size of albuterol emitted from a Volumatic VHC with the amount of net electrostatic charge determined using a field-sensing probe located at the mid-point of the device.²² The fine-particle ($< 6.8 \mu\text{m}$) fraction decreased systematically, from close to 35% with no voltage within the VHC (charge neutral) to just over 10% when the static voltage was close to 17 kV (the largest value measured). Several other groups have also observed large decreases in drug output with electrostatically charged VHCs. For example, Barry and O’Callaghan found that coating the inside of a polycarbonate Nebuhaler VHC with an antistatic lining increased the fine-particle ($< 5 \mu\text{m}$) mass of pMDI budesonide from $30.5 \pm 8.8 \mu\text{g}/\text{actuation}$ (untreated device) to $69.3 \pm 17.9 \mu\text{g}/\text{actuation}$.⁵⁷ They also reported similar behavior with sodium cromoglycate via the Fisonair large-volume polycarbonate VHC, using a commercially available anti-static aerosol spray to line the chamber interior.⁵⁸ Shortly afterwards, Wildhaber et al reported a 40% reduction in fine-particle ($< 6.8 \mu\text{m}$) albuterol from Volumatic VHCs that had been stored in their original plastic bags (ie, with no pre-washing), compared

with that emitted from devices covered on the inside with aluminum foil to eliminate surface charge (ie, minimize the electric potential at the surface).⁵⁴ In separate measurements, using an electrometer, they found that new devices had high electrostatic charge, compared with no detectable charge in the foil-coated VHCs. Still more recently, Churfart et al showed that removal of electrostatic charge from Nebuhaler and Volumatic VHCs, as well as from a smaller polyester VHC (AeroChamber) increased the mass of both CFC and HFA albuterol, by 17–82%.¹⁵

In the mid-1990s, when electrostatic medication loss initially became apparent to clinicians, Jackson and Lipworth proposed developing a strategy to improve the performance of add-on devices, with the objective of minimizing the number of inhalations needed to achieve the desired response.⁵⁹ At about the same time, Barry and O’Callaghan observed that a Volumatic that has been used and washed typically has less charge than a new Volumatic.⁶⁰ Similar behavior was reported by Kenyon et al, who “primed” their VHCs by delivering 20 actuations of a placebo that contained only surfactant particles, before use with the active pharmaceutical formulation.⁶¹ Both investigations found that as the inner walls become coated with

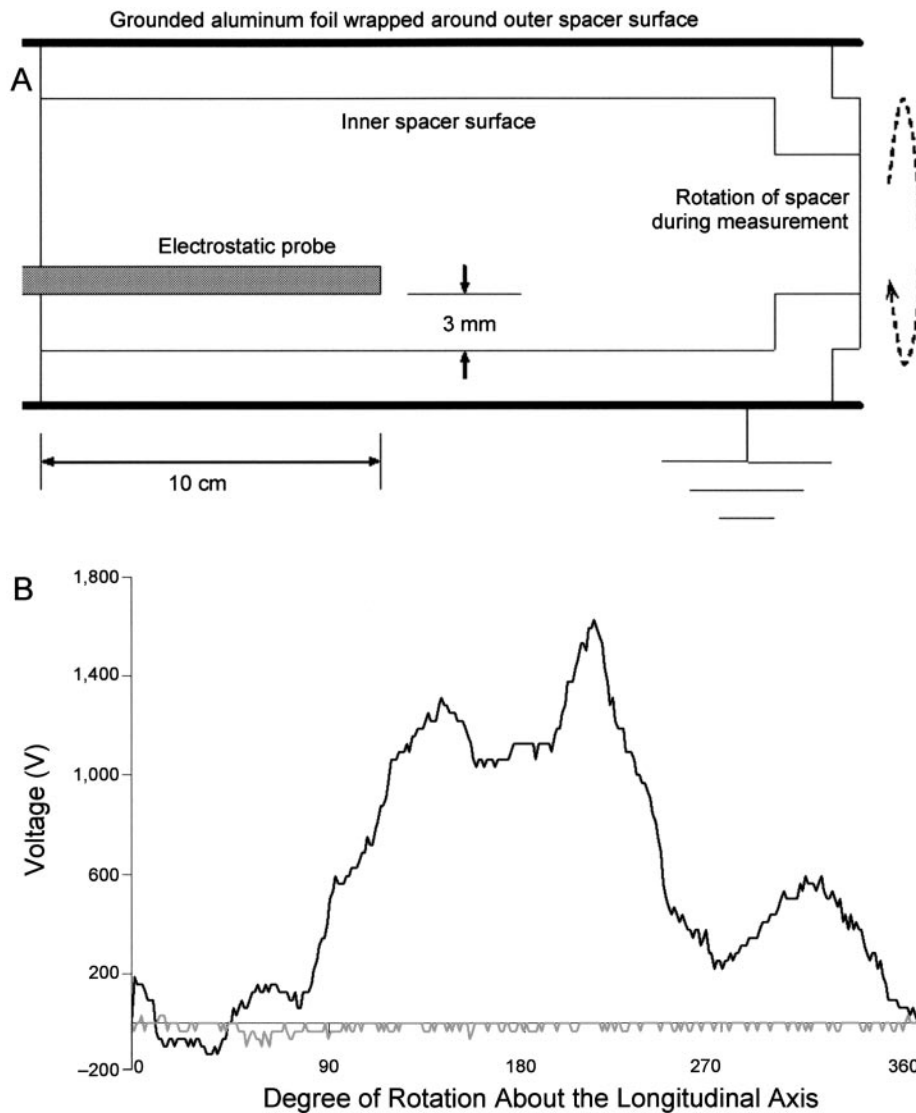


Fig. 6. A: Schematic of a setup to measure the surface potential inside a valved holding chamber. B: Surface potential on the inner circumference of a new (black line) and detergent-coated (gray line) nonconducting valved holding chamber. (Both adapted from Reference 24, with permission.)

drug particles and/or surfactant (which is an excipient in many formulations), the polymer surface becomes conditioned with an electrically conducting layer that reduced overall charge. This wall-coating phenomenon is linked with inconsistent medication delivery, which might not be readily apparent to the clinician and leading to potential under-dosing.

Washing a nonconducting VHC with detergent is a widely used method to alleviate surface electrostatic charge, and detergent-washing is now incorporated in most manufacturer instructions. Detergent-washing greatly improves drug delivery at the patient interface (face mask or mouth-piece), and is easy for the patient to perform.^{51,54} However, it requires that the patient or provider remembers to

perform the procedure, both when new and as part of regular cleaning.

Surfactants such as short-chain fatty acids and alcohols are soluble in both aqueous and nonaqueous (oil-like) media, because they have a nonpolar hydrocarbon lipophilic core combined with a polarizable or ionic hydrophilic portion at one end.⁶² Detergents of all types can spread onto surfaces to form a coating that can be as thin as a monomolecular layer.⁶² Although the precise mechanism has not yet been established at the molecular level, it is likely that the hydrophilic portion of the surfactant molecules enables the conduction of surface electrostatic charge away from the chamber walls, via the user, to ground. Most synthetic detergents have a negative ionic group, typically

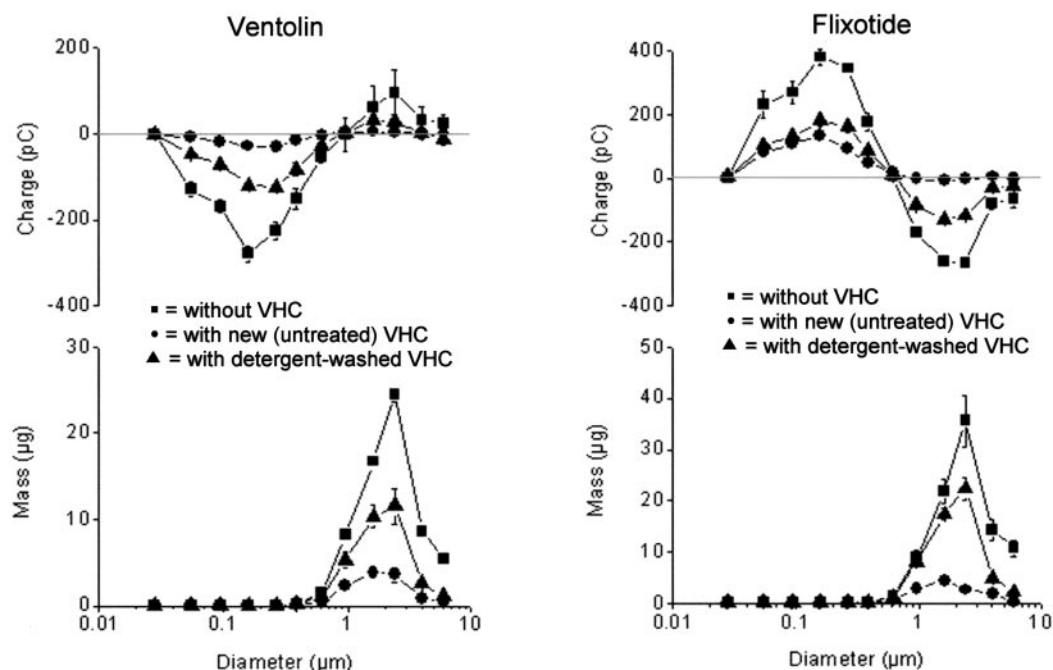


Fig. 7. Mean charge and mass of Ventolin and Flixotide aerosols, without a valved holding chamber (VHC) (■), with an untreated new VHC (●), and with a detergent-coated VHC (▲). (From Reference 24, with permission.)

an alkyl sulfate structure, and are thus anionic. A cationic detergent has a positive ionic group, typically a quaternary ammonium structure. A third class of detergent (eg, pentaerythrityl palmitate) contains polarizable components within the structure of the molecule, but the molecules are not ionized (nonionic detergent).

Reduction in surface electrostatic charge by coating the VHC with detergent was recently demonstrated by Kwok and Chan.²⁴ They also compared the charge/size profiles of HFA Ventolin and Flixotide-250 emitted from VHCs newly removed from their packaging versus after pre-washing with detergent, followed by drip-drying in air at room ambient conditions.²⁴ The new devices had greater charge and lower drug mass, compared with the pMDI alone, but the charge/size profiles were insignificantly affected, which suggests a size-independent process (Fig. 7). Detergent-washing decreased drug mass retained per actuation in the VHC, from slightly above label claim (100 μg) at $113.6 \pm 23.7 \mu\text{g}$ to $66.0 \pm 13.6 \mu\text{g}$ for Ventolin, and from $233.7 \pm 16.5 \mu\text{g}$ to $156.5 \pm 13.9 \mu\text{g}$ for Flixotide (250 μg label claim).

In a more systematic assessment of detergent-washing VHCs, Wildhaber et al explored the chemical nature of the detergent and its effect on charge reduction, using Volumatic VHCs. They compared unwashed Volumatics with Volumatics washed with either cationic or anionic detergents and drip-dried in air, and found as much as 70% greater fine-particle delivery of albuterol with the washed VHCs.⁵⁴ In a follow-up study, Piérart et al confirmed that

Table 4. Fine-Particle Percentage of Albuterol Emitted From Untreated and Detergent-Washed Nonconducting Small-Volume VHCs

Condition	Fine-Particle Percentage* (mean \pm SD %)		
	Babyhaler	Babyspacer	AeroChamber
Static (no pretreatment)	32.9 \pm 1.4	30.3 \pm 2.9	32.1 \pm 2.1
Reduced static (pre-washed in ionic detergent)	56.3 \pm 2.1	44.4 \pm 1.4	47.9 \pm 2.0
Percentage difference	71.1	46.5	49.2

*Percentage of the total actuated mass emitted as fine particles (<6.8 μm aerodynamic diameter)
VHC = valved holding chamber
(Data from Reference 63.)

behavior with similar VHCs that had been pre-washed with one of several types of anionic or cationic detergent.⁵¹ A wide range of detergent concentrations (range 1:125 to 1:10,000) resulted in similar fine-particle (< 6.8 μm) mass of albuterol. That suggests that the detergent concentration is not important, so the instructions for detergent-washing need only specify “a few drops of detergent in water.”

In a further investigation, Wildhaber et al observed similar increases (47–71%) in fine-particle albuterol delivery from smaller (135–350-mL) nonconducting, polycarbonate and polyester, detergent-washed VHCs (Table 4).⁶³

Interestingly, in their original study they found that improvement was largely independent of detergent type (cationic or anionic) and was maintained after 24 hours of drip drying.⁵⁴ If the devices were stored for up to a week, either in plastic bags or in the open, total net charge (measured by a Faraday cup electrometer) increased but was still lower than that in new devices. However, although non-ionic detergent improved medication delivery, compared with untreated devices, the beneficial effect was reduced. Low but important charge was detectable with these devices after 2 hours of drip-drying and built up to a higher level after 24 hours.

In some jurisdictions, particularly the United States, regulators require manufacturers of add-on devices to rinse them in clean water after washing them in detergent, to avoid patient contact with detergent-coated surfaces. However, Piérart et al⁵¹ also observed that rinsed, drip-dried Volumatic VHCs had substantial electrostatic charge and lower albuterol fine-particle ($< 6.8 \mu\text{m}$) delivery: mean \pm SD range $50.1 \pm 4.0\%$ to $53.1 \pm 3.1\%$ of the label claim emitted mass/actuation with detergent-coated devices, versus $36.2 \pm 3.5\%$ with rinsed VHCs.

Although manufacturers generally instruct users to wash and dry the VHC before use, to mitigate electrostatic loss of medication,³ the need to pre-wash an already clean device complicates its use. Furthermore, these instructions may not always be followed in the emergency setting, where time may be of the essence in treating an exacerbation of obstructive disease. The use of devices made from conducting materials, such as stainless steel,^{64,65} avoids the problem altogether. Bisgaard reported that the half-life (time for the aerosol concentration to decay to 50% of the peak value) was > 30 s with a stainless steel VHC (NebuChamber), compared with only 9 s with a VHC manufactured from a nonconducting material (Nebuhaler) that had not been pretreated in any way.⁶⁴ However, with a metallic-walled VHC it is impossible to see the formation of the aerosol plume, which informs the patient or provider that the medication was delivered.⁶⁶ A solution to this problem was the recent development of VHCs made from charge-dissipative polymers that are transparent but also rapidly dissipate electrostatic charge, because of their in-built polarizable molecular structure.⁶⁷ These charge-dissipative polymers contain a variety of proprietary compounds in their chemical structure that increase bulk electrical conductivity, such that they typically have surface resistivity values in the range of 10^5 – 10^{10} ohm (volume resistivity between 10^4 – 10^{11} ohm-cm), compared with insulators, whose surface resistivity is in excess of 10^{12} ohm (volume resistivity $> 10^{11}$ ohm-cm).⁶⁸ Such VHCs enable comparable medication delivery regardless of pre-washing.^{69,70} For instance, Coppolo et al found that mean fine-particle ($< 4.7 \mu\text{m}$) delivery of levalbuterol was $36.3 \pm 1.1 \mu\text{g/actuation}$ with a charge-dissipative VHC

Table 5. Fine-Particle Percentage of Albuterol Emitted From an Untreated Versus a Pretreated (Detergent-Washed) Babyhaler Nonconducting, VHC, With and Without Inhalation Delay

Inhalation Delay (s)	Fine-Particle Percentage* (mean \pm SD)	
	Untreated	Detergent-Washed
0	32.9 ± 1.5	56.3 ± 2.0
1	19.5 ± 1.9	57.2 ± 1.4
5	12.3 ± 0.6	55.2 ± 1.5
20	8.6 ± 1.0	53.7 ± 1.2

*Percentage of the total actuated mass emitted as fine particles ($< 6.8 \mu\text{m}$ aerodynamic diameter)

VHC = valved holding chamber
(Data from Reference 63.)

removed from its polymer packaging immediately before testing, compared with $33.5 \pm 1.4 \mu\text{g/actuation}$ with the same device detergent-washed and rinsed.⁶⁹

Minimizing electrostatic charge can be critical with patients who delay aerosol inhalation after actuation, as frequently occurs.^{71,72} In the mid-1990s, Wildhaber et al found that fine-particle delivery of albuterol from several different small-volume, nonconducting, polycarbonate Babyhaler VHCs was adversely affected by delayed inhalation and positively affected by detergent washing (Table 5). The untreated VHC had a mean fine-particle percentage of $32.9 \pm 1.45\%$ with no delay, versus $12.3 \pm 0.58\%$ with a 5-s delay, whereas the detergent-washed VHC's value was $56.3 \pm 2.05\%$ with no delay and $55.2 \pm 1.49\%$ with a 5-s delay. More recently, Rau et al, in a study with several untreated, nonconducting VHCs, also found that albuterol delivery is significantly compromised with a delay as short as 2 s between actuation and the onset of simulated inhalation (Table 6).⁷⁰

Given the importance already established of detergent-washing VHCs, we might anticipate that nonconducting VHCs would perform poorly without pretreatment, so it was an unexpected finding that there were only very small improvements in fine-particle mass after following manufacturer instructions to detergent-wash and rinse (see Table 6). However, in retrospect, these findings, taken with the observations by Piérart et al⁵¹ in connection with rinsing, support the conclusion that a wash-rinse protocol may not provide adequate protection against electrostatic charge, which may result in inconsistent medication delivery.

The use of charge-dissipative or conducting materials also appears to benefit dose reproducibility when the VHC is used with a face mask, as is often practiced with infants, small children, and adults with poor hand-mouth coordination. Thus, the data reported by Janssens et al, in a clinical trial in which 17 children (1–4 years old) with

Table 6. Fine-Particle Mass of Albuterol, With and Without Detergent-Wash Pretreatment, With 2-s Versus 5-s Inhalation Delay

Valved Holding Chamber	Material Type	Fine-Particle Mass* (mean \pm SD μ g)			
		2-s Inhalation Delay		5-s Inhalation Delay	
		No Pretreatment	Pretreated	No Pretreatment	Pretreated
AeroChamber Max	Charge-dissipative	23.8 \pm 4.8	21.5 \pm 3.2	19.1 \pm 2.1	18.6 \pm 1.8
Vortex	Charge-dissipative/conducting	16.2 \pm 1.7	15.5 \pm 2.0	12.7 \pm 1.4	11.4 \pm 2.7
OptiChamber Advantage	Nonconducting	2.6 \pm 1.2	6.7 \pm 2.3	1.0 \pm 0.1	2.3 \pm 1.3
ProChamber	Nonconducting	1.6 \pm 0.4	5.1 \pm 2.5	0.9 \pm 0.5	1.5 \pm 0.3
Breathrite	Nonconducting	2.0 \pm 0.9	3.2 \pm 1.8	0.5 \pm 0.5	0.4 \pm 0.4
Pocket Chamber	Nonconducting	3.4 \pm 1.6	1.7 \pm 1.6	1.0 \pm 0.7	0.4 \pm 0.5
ACE	Nonconducting	4.5 \pm 0.9	5.4 \pm 2.9	3.2 \pm 0.8	2.9 \pm 1.4

*Mass of aerosol emitted as fine particles ($<4.7 \mu$ m aerodynamic diameter)
(Data from Reference 70.)

stable asthma were asked to inhale from VHCs made from either conducting or nonconducting materials, indicate that electrostatic charge can affect drug delivery.⁷³ In that study, pMDI budesonide was collected on a filter between the face mask and the patient's mouth. The mean \pm SD filter dose (ie, the mass emitted at the patient interface), as a percentage of the nominal dose, was significantly higher with the conducting NebuChamber (41.7 \pm 10.1%) than with the washed and rinsed, nonconducting Babyhaler (26.0 \pm 4.0%). Although some of the difference in drug delivery may have been due to differences in VHC design, the lower output with the Babyhaler may have been due to removal of detergent by rinsing, since they observed a small but significant priming effect (increasing 0.8% per day, equivalent to 0.4% per consecutive sample) with the rinsed Babyhalers, but not with the metal NebuChambers.

More recently, Louca et al,⁷⁴ in a laboratory study using an anatomically correct model of a 1-year-old infant face,⁷⁵ simulated tidal breathing via VHC with face mask. They found that the delivery efficiency (total emitted mass as a percentage of total actuated mass) of HFA fluticasone propionate via the charge-dissipative AeroChamber Max, whether rinsed or not, was significantly greater than either of 2 nonconducting VHCs washed in ionic detergent but not rinsed (Table 7). The variability associated with either type of pretreatment for the charge-dissipative VHC was similar, which indicates that these devices do not need preconditioning before use.

Clinical Implications

To date, the focus on clinical implications of electrostatic charge with add-on devices has been the effect on performance, rather than on the inhaler itself. This is largely because almost all spacers and VHCs were, until recently, manufactured from nonconducting polymers, and there-

Table 7. Aerosol Delivery Efficiency With HFA-Propelled Fluticasone Propionate to an Infant Face Model Via 3 Types of VHC With Face Mask

	AeroChamber Max*		OptiChamber Advantage	ProChamber
	Untreated	Detergent-Washed and Rinsed	Detergent-Washed But Not Rinsed	
Delivery Efficiency (mean % of nominal dose, 95% CI)	22.0 (0.7)	21.2 (1.5)	8.8 (1.9)	10.2 (0.55)

*AeroChamber Max is made of charge-dissipative material
HFA = hydrofluoroalkane
VHC = valved holding chamber
CI = confidence interval
(Data from Reference 74.)

fore vulnerable to charge accumulation. It is also relatively straightforward to investigate the clinical effect of electrostatic charge on VHC performance, in comparison studies. The large improvement in emitted medication delivery from pMDIs with VHCs either pre-washed with detergent or manufactured from materials that do not retain electrostatic charge raises the question: Is this increase in output associated with clinical consequences when treating lung diseases such as asthma or chronic obstructive pulmonary disease? Rau, in a recent review of practical issues associated with therapy for chronic obstructive pulmonary disease, commented that, although decreased output from add-on devices can be compensated for by priming the device with multiple actuations of medication before use, that practice wastes medication.⁷⁶ This position is also borne out in a recently issued Canadian clinical guidance on pediatric asthma.⁷⁷ However, priming may only be effective with formulations that contain surfactant. Rau's

observations were based on a gamma scintigraphy study by Kenyon et al,⁶¹ who used radiolabeled budesonide in 10 mildly asthmatic adults. Priming the Nebuhaler and Volumatic large-volume nonconducting VHCs with 20 actuations of placebo to coat the interior surfaces with surfactant increased whole-lung deposition (expressed as a percentage of the metered dose) by a mean \pm SD $37.7 \pm 12.0\%$ primed versus $26.7 \pm 6.2\%$ not primed with the Nebuhaler, and by $32.0 \pm 10.8\%$ primed versus $22.1 \pm 10.1\%$ not primed with the Volumatic.

Delivering additional doses at fixed intervals greater than about 30 s via an untreated and electrostatic charged device to condition the interior surfaces with drug particles and surfactant so as to reduce charge and achieve the desired clinical response may be a practical alternative with relatively low-cost medications such as albuterol. However, that is an off-label use, and adverse effects, such as tachyarrhythmia, have been reported in mechanically ventilated patients with this approach.⁷⁸ Furthermore, the amount of electrostatic charge may vary widely from one treatment to the next, depending on environmental conditions, especially relative humidity.²⁷ Such variability increases the risk of under-dosing if the clinician bases the dose decision on laboratory or clinical performance data that might have been obtained under conditions where steps had been taken to eliminate or minimize electrostatic charge.

The potential to improve medication delivery by detergent-washing or by constructing the VHC from conductive/charge-dissipative material is well established by the above-described laboratory studies. In terms of lung-deposition measurements, the effect of detergent-washing the VHC on lower-lung drug deposition was studied by Wildhaber et al, with 18 children with stable asthma.⁷⁹ Using gamma scintigraphy, they found that a mean \pm SD $16.4 \pm 5.5\%$ of the actuated dose was lung-deposited in younger children, age < 48 months (group A), whereas in older children (age 48–146 months), who had different breathing patterns, the mean lung deposition was $28.2 \pm 6.7\%$ in group B and $41.8 \pm 3.8\%$ in group C, when the aerosol was delivered via detergent-treated (but not rinsed) nonconducting VHC (group A used Babyhaler, groups B and C used Volumatic). Another study by Wildhaber et al gave further support for improved clinical efficacy with detergent pre-treatment. The dose of bronchodilator required to elicit a 10% improvement in forced expiratory volume in the first second was less when using a pre-treated (versus an untreated) Volumatic. In 20 adults with stable asthma and a known bronchodilator response, a dose of $430 \pm 732 \mu\text{g}$ was required with the treated VHC, whereas with the untreated VHC a dose of $1,505 \pm 1,335 \mu\text{g}$ was required.⁵²

After preconditioning, at least one clinical guideline for asthma counsels against towel-drying the VHC, because

towel-drying could impart electrostatic charge; instead, allow the VHC to drip-dry in ambient air.⁸⁰

The effectiveness of an electrically conducting stainless-steel-walled VHC, as an alternative to a detergent-washed nonconducting device, was borne out by lung-deposition measurements with technetium-labeled budesonide, by Kenyon et al.⁶¹ They observed high values of whole-lung deposition, expressed as a percentage of the label claim dose, with the NebuChamber metal VHC (mean \pm SD) of $33.5 \pm 12.7\%$, that were comparable to 2 other nonconducting VHCs that had been primed with 20 actuations of a formula that contained surfactant but no active pharmaceutical ingredient (Nebuhaler $37.7 \pm 12\%$, Volumatic $32.0 \pm 10.8\%$). However, the corresponding lung-deposition values for Nebuhaler and Volumatic VHCs that were not primed (but instead evaluated immediately after removal from their packaging) were only $26.7 \pm 6.2\%$ and $22.1 \pm 10.1\%$, respectively, compared with a negligible decrease with the NebuChamber when treated in the same way ($32.9 \pm 10.1\%$). These observations are supported by the consistently high delivery efficiency of the NebuChamber, compared with nonconducting VHCs with pMDI budesonide, in the study by Janssens et al.⁷³ Their daily-life study with small children with stable asthma provided further evidence that untreated nonconducting VHCs may result in unpredictable dose delivery.

VHCs manufactured from transparent, charge-dissipative polymers, as an alternative to opaque conducting materials such as stainless steel or aluminum, have become available only within the last few years. Asmus et al, in a study with 12 children with stable asthma (ages 1.3–6.8 years), measured serum fluticasone propionate as a surrogate for lung deposition. One hour after administering fluticasone propionate via a charge-dissipative transparent small-volume VHC (AeroChamber Max), the mean \pm SD serum fluticasone propionate concentration was $185.6 \pm 134.3 \text{ pg/mL}$, compared with $106.9 \pm 29.5 \text{ pg/mL}$ when administered via a nonconducting and slightly smaller VHC.⁸¹ There was large inter-patient variability, which highlights the need to titrate the dose to the individual, regardless of the type of VHC used, as recommended in current asthma guidelines.^{1,82,83}

The position statement provided by Le Souëf in 2002, concerning delivery of inhaled corticosteroids and β agonists to asthmatic children via pMDI with an add-on device⁸⁴ is helpful for understanding the clinical importance of electrostatic-charge-related effects on drug delivery consistency with VHCs. In his opinion, the increase in performance associated with detergent pretreatment of devices manufactured from nonconducting materials is almost certainly important for inhaled corticosteroids, and is likely to substantially improve therapy in some children but also to increase the risk of steroid toxicity in others. This further supports the need to titrate the dose to the patient on

an individual basis. However, note that Amirav et al investigated hypothalamic-pituitary-adrenal axis suppression in 30 children treated with budesonide (200 μg , twice daily, in a simulation of real-life use for a 4-week period) and found that the metallic NebuChamber VHC was not associated with significantly greater hypothalamic-pituitary-adrenal suppression than was treatment via non-conducting VHC.⁸⁵

Le Souëf indicated that for inhaled β agonists, with which the dosage is much less critical and toxicity is a relatively minor issue, the improvement in delivery may not be as important clinically.⁸⁴ His observations concerning β agonists are based in part on the findings of Dompeling et al,²³ who found that differences in bronchodilating effect (peak expiratory flow) were insignificant in children given HFA albuterol via 2 nonconducting VHCs pre-washed with ionic detergent, compared with the bronchodilation response with a stainless steel VHC. However, Dompeling et al acknowledged 2 limitations that may have accounted for the lack of a difference. First, the children tested had excellent inhaler technique; they began inhalation with minimal or no delay after actuation. Second, their peak expiratory flows may have already reached the plateau at the high end of the dose-response curve.

Dubus et al⁸⁶ also found little difference in clinical outcomes (specific airway resistance and forced expiratory volume in the first second) in a pharmacodynamic study with 64 children with moderately provoked bronchial obstruction following methacholine challenge, when treated with the same β agonist as used by Dompeling et al. However, they also acknowledged that their patients were at the plateau of the dose-response curve following administration of 100 μg albuterol, followed 15 min later by 2 additional 100- μg doses. They further observed that methacholine challenge does not mirror an asthma attack.

In contrast to the latter 2 studies, Anhøj et al had proposed avoiding the use of charged VHCs, based on their observation that the electrostatic charge associated with either of 2 different nonconducting VHCs reduced lung deposition by more than two-fold in 5 children (2 of whom were mildly asthmatic), ages 7–12 years, and was associated with significant decreases in plasma albuterol concentration.⁸⁷

Taking all the above considerations into account, it is evident that electrostatic charge increases the variability of medication delivery. If a nonconducting VHC is used, the clinician should be aware that electrostatic phenomena will probably reduce drug-delivery consistency and increase the risk of erratic dosing. However, even when greater control is obtained by pre-washing or using a conducting/charge-dissipative VHC, the clinician should still follow current asthma guidelines^{1,82,83} and titrate to the lowest dose that effectively controls the symptoms, particularly with corticosteroids.

Conclusions

The acquisition of electrostatic charge during the generation of pMDI aerosols, combined with the surface charge on electrically insulating VHC surfaces, can severely impact the consistency of medication delivery. Charge-related medication losses are exacerbated by the add-on devices that are widely used in the treatment of obstructive lung disease. The problem is exacerbated by delayed inhalation after actuation, which is one of the main reasons for prescribing a VHC in the first place.

Laboratory and clinical evidence both strongly support detergent-washing of add-on devices, followed by drip-drying (do not towel dry). Rinsing the detergent-washed VHC is advocated by some regulatory agencies to avoid contact dermatitis from the detergent, but rinsing removes some of the detergent from the VHC surface and thereby decreases the protection against electrostatic charge. Rinsing only the mouthpiece or face mask may therefore be considered, to avoid the loss of protection against electrostatic charge.

Although the use of an electrically conducting, metallic VHC obviates detergent-washing, a metal VHC is not transparent, so the patient and/or clinician can not see the creation and delivery of the aerosol plume, which can affect patient adherence to treatment. Manufacturing the VHC from a charge-dissipative polymer provides both transparency and electrical conductivity. In vitro testing indicates that, compared with metal VHCs, charge-dissipative-polymer VHCs confer similar benefit in medication delivery at the mouthpiece or face mask. However, given the lack of studies on the risk of under-dosing caused by electrostatic charge, the clinician should titrate the dose to individual patient response, as advocated by current asthma guidelines, whatever VHC or pretreatment protocol is used. Future studies are warranted to assess the clinical benefits of charge-dissipative and electrically conducting VHCs that are implied by laboratory data.

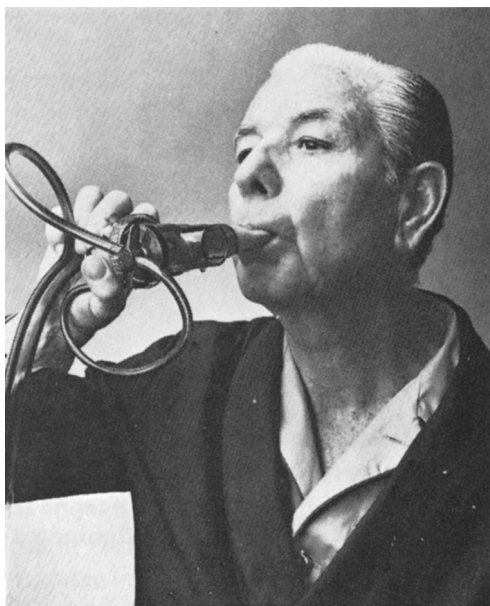
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